CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020884

MEDICAL REVIEW(S)

DuBois

NOV - 9 1999

Division of Gastrointestinal and Coagulation Drug Products

Medical Officer's Review

NDA:	20-884 BL dated 11/4/99
Sponsor:	Boehringer Ingelheim
Drug Product:	Aggrenox™
Date submitted:	November 4, 1999
Date Received:	November 5, 1999
Date assigned:	November 8, 1999
Review Completed:	November 8, 1999
Reviewer:	Ann T. Farrell MD

Background:

The sponsor is seeking approval of Aggrenox™ (dipyridamole 200mg/aspirin 25 mg) for marketing "to reduce the risk of stroke in patients who have had transient ischemia of the brain or completed stroke due to thrombosis". On June 15, 1999 an approvable letter for this indication was sent. The letter included requested revisions to the proposed labeling. The sponsor submitted for review a revised label for Aggrenox™ in submission BL dated August 6, 1999. The Agency reviewed this proposed label and had 5 recommendations for the clinical sections of the label.

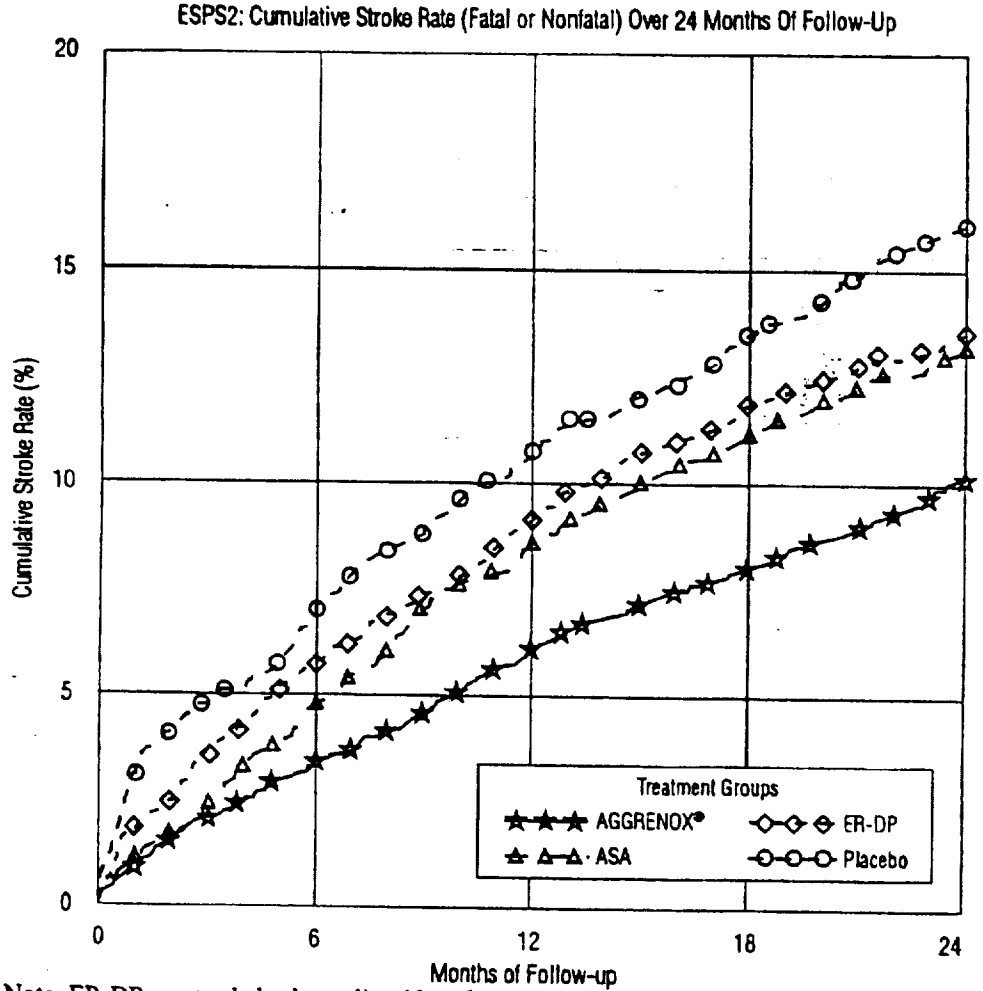
The sponsor was requested to:

1. Under the clinical trials section, revise Figure 1.
2. Revise the subsection regarding the Death Endpoint to read,
3. Revise the CONTRAINDICATIONS section to include verbatim all the contraindication wording in the aspirin label.
4. Revise the Pediatric Use section to include a statement to see the contraindications section of the label.
5. Revise the Overdosage section to add the following statement in section 86.
6. Choose between the phrases

The sponsor has submitted this revised labeling for Aggrenox™ in response to Agency comments concerning the clinical section of the label. The sponsor has also responded to comments from

the FDA pharmacology and the biopharmaceutics reviewers. This review concerns the proposed revision to the clinical section.

1. The firm has submitted a new graph titled Figure 1 which is shown below.
Sponsor's graph



Note: ER-DP – extended-release dipyridamole 200 mg; ASA – aspirin 25 mg.
Note: The dosage regimen for all treatment groups is b.i.d.

There are no objections to this graph. This graph is acceptable.

2. Below is the sponsor's latest revision for the Death Endpoint section:

The references to previous aspirin studies, approved aspirin labeling, and the observed risk reduction statements should be removed.

The recommended Death Endpoint subsection is:

DRAFT LABELING

3. The contraindications section was rewritten as requested by the Agency to include information on Reye's syndrome in teenagers. The changes are acceptable.

4. Under the Pediatric Use subsection, the sponsor has made a reference to the contraindications section of the label. This change is acceptable.

5. Under the Overdosage section the sentence "Careful Medical management is essential" has been added. This change is acceptable.

6. The sponsor was requested to choose either the word "liver" or "hepatic" and use it consistently throughout the label. They have chosen the word "hepatic" and have made changes accordingly. These changes are acceptable.

The sponsor has also revised the label for the adverse events section. For adverse events that occurred in less than 1% of patients treated with Aggrenox™ in the ESPS2 study, the sponsor proposes to use the same format as the Plavix label. Below is the sponsor's proposal:

Other adverse events:

DRAFT

LABELING

The following is a list of adverse events that have been reported either in the literature or are from postmarketing spontaneous reports for either dipyridamole or aspirin. The causal relationship of these adverse events has not been established: anorexia, aplastic anemia, pancytopenia, thrombocytosis.

These changes concerning the adverse events are acceptable to the Agency.

Reviewer's Conclusions and Recommendations

The sponsor has submitted the latest revised labeling for Aggrenox™ to the Agency. With one exception, the proposed changes to the clinical section are acceptable. The sponsor needs to revise the Death Endpoint section of the label so that it reads:

DRAFT LABELING

This recommendation should be conveyed to the firm.

/S/

Ann T. Farrell, M.D.

11/9/99

cc:
NDA 20-884
HFD-180
HFD-180/LTalarico /S/ 11-9-99
HFD-180/SAurecchia
HFD-180/KRobie-Suh
HFD-180/AFarrell
HFD-181/JDuBeau
HFD-180/JChoudary
HFD-180/LZhou
f/t 11/9/99 jgw
N/20884911.0AF

APPEARS THIS WAY
ON ORIGINAL

Duran

OCT 12 1999

Division of Gastrointestinal and Coagulation Drug Products

Medical Officer's Review

NDA:	20-884 BL dated 8/6/99, BZ dated 8/20/99
Sponsor:	Boehringer Ingelheim
Drug Product:	Aggrenox® (dipyridamole/aspirin)
Date submitted:	August 6, 1999, August 20,1999
Date Received:	August 9, 1999, August 23, 1999
Date assigned:	August 17, 1999, August 23,1999
Review Completed:	October 5, 1999
Reviewer:	Ann T. Farrell MD

Background:

The sponsor is seeking approval of Aggrenox® (dipyridamole 200mg/aspirin 25 mg) for marketing "to reduce the risk of stroke in patients who have had transient ischemia of the brain or completed stroke due to thrombosis". On June 15, 1999 an approvable letter for this indication was sent. The letter included Biopharmaceutics issues that needed to be addressed and requested revisions to the proposed labeling. The approvable letter also referred to letters from the Division on May 26, 1999 and June 4, 1999 identifying CMC issues and Pharmacology issues, respectively, that need to be addressed. The sponsor has submitted for review a revised label for Aggrenox® in submission BL dated August 6, 1999 and narrative responses to the Agency's approvable letter in submission BL dated August 20, 1999. Both of these submissions have been reviewed.

Reviewer's Comments:

In the August 6, 1999 submission, the sponsor has divided most of the label into 102 sections for ease of comparison and revision. This review uses those section numbers.

(1). Changes in sections 2-9, 61-76, 93, and 96-98 will be addressed by the FDA chemistry review.

(2). Changes in sections 10-27 and 61-76 will be addressed by the FDA pharmacology, and biopharmaceutics reviews.

(3). The changes proposed for sections 1, 28, 29, Table 1, 31-34, 36-60, 77-85, 87-92, 94, 95, and 99-102 are acceptable.

(4). Under the clinical trials section, the sponsor has reinserted Figure 1 (page 15 of the August 8, 1999 submission), which was deleted in our first review of the label. The figure shows Kaplan-Meier estimated stroke-free survival. The sponsor has titled the figure "Study ESPS2: Percentage of Patients Remaining Stroke Free Over 24 Months". The figure was deleted originally because it was felt that the graph was misleading with the y-axis starting at 0.75 and it was somewhat redundant given the table before it. The figure may be included only if the following conditions are met. First the y-axis must be changed to reflect origin at 0.00. Second, the title of the figure and the associated text needs to reflect the fact that it is generated from Kaplan-Meier survivor function analysis.

(5). Section 30: The sponsor has rewritten section 30 from a meta-analysis of aspirin and the aspirin labeling to include "a small non-significant reduction in mortality". The proposed revision is not acceptable. The results presented in the clinical trial section should reflect results obtained in the pivotal clinical trial not results based on the meta-analysis and aspirin labeling. The sponsor should replace the proposed wording with the following: "Death Endpoint: No statistically significant difference was observed among the three treatment arms compared to placebo for the endpoint of death from all causes."

(6). Section 35: The sponsor was requested to rewrite the CONTRAINDICATIONS section of the label to include verbatim all the contraindications section in the aspirin labeling since this product contains aspirin. This has not been done. The sponsor should be redirected to comply with the recommendations.

(7). The sponsor uses the following phrases in different sections:

Section number	Phrase
42	Elevated liver enzymes
46	Elevated hepatic enzymes
47	Elevated liver enzymes

Reviewer's table

The sponsor should be asked to choose between the word "liver" or "hepatic" for consistency in the label and to avoid any confusion.

(8). Section 76: At the end of the Pediatric Use section the sponsor should include a cross-reference to see the Contraindications section of the label.

(9). Sections 86 and 88: The sponsor has moved the statement "In case of real or suspected overdose, seek medical attention or contact a Poison Control Center immediately." from the aspirin subsection of the Overdose section to the introductory paragraph (section 86) but has deleted the next sentence "Careful medical management is essential." The sentence, "Careful medical management is essential", should be placed in the introductory paragraph immediately following the statement about the Poison Control Center.

Conclusions and Recommendations:

The sponsor's proposed changes are acceptable except as follows. Section numbers refer to sections in the sponsor's draft labeling in the August 6, 1999 submission.

The sponsor should:

1. Under the clinical trials section, in Figure 1 revise the y-axis to reflect origin at 0.00. The title of the figure and associated text should reflect the fact that it is generated from Kaplan-Meier survivor function statistics.

2. Revise section 30 to read,

3. Revise section 35 to include verbatim all the contraindication wording in the aspirin label.

4. Revise section 76 to include a statement to see the contraindications section of the label.

5. Add the following statement in section 86,

6. Choose between the phrases and use one phrase consistently throughout the label.

These comments should be conveyed to the sponsor.

/S/
Ann T. Farrell, M.D.

cc:
NDA 20-884
HFD-180
HFD-180/LTalarico
HFD-180/SAurecchia
HFD-180/KRobie-Suh
HFD-180/AFarrell
HFD-181/JDuBeau
HFD-180/JChoudary
HFD-180/LZhou
f/t 10/12/99 jgw
N/20884910.0AF

/S/ 10-12-99

10/12/99

APPEARS THIS WAY
ON ORIGINAL

Division of Gastrointestinal and Coagulation Drug Products

Medical Officer's Review

MAY 13 1999

NDA:	20-884[1.001-1.147]
Sponsor:	Boehringer Ingelheim Pharmaceuticals, Inc.
Drug Product:	AGGRENOX™ (extended release dipyridamole 200 mg/aspirin 25 mg) capsules
Sponsor's Indication:	
Date submitted:	December 15, 1998
Date Received:	December 17, 1998
Date assigned:	December 23, 1998
Amendments dated:	1/19/99,1/21/99,1/25/99,1/27/99,3/8/99,4/15/99
Review Completed:	April 30, 1999
Reviewer:	Ann T. Farrell MD

APPEARS THIS WAY
ON ORIGINAL

Materials Reviewed

A total of 147 volumes were submitted.

Volume number	Content
1.001	Index, 356h,Cover letter, letter of authorization, user fee form, reviewer's guide, patent information, exclusivity information, certificate of debarred persons, confidentiality statement
1.002	Labeling
1.003	Application Summary, Development Program, Marketing History
1.004-1.018	Chemistry, Manufacturing, and Controls
1.019-1.053	Nonclinical Pharmacology and Toxicology
1.054-1.076	Human Pharmacokinetics and Bioavailability
1.077-1.086	Clinical guide, Development program, Summary of ESPS2 and ESPS1, Integrated Summary of Benefits and Risks, Drug Abuse/Overdose Potential, GCP Statement, Summary of Clinical Pharmacology Studies, FDA Medical Officer's Review of Ticlopidine, Literature review
1.087-1.089	Efficacy data for ESPS2, literature review
1.90-1.105	Safety Data for ESPS2, Data Handling of Safety Data, Appendices, Definitions of Adverse Events, Serious Adverse Events, Narratives listings
1.106	References for low dose aspirin
1.107-1.109	Unpublished report for U88-0473, ESPS1 clinical trials report
1.110-1.112	Pharmacokinetic Trials and data
1.113	Pharmacokinetics for ESPS2
1.114-1.115	Amendments to ESPS2 clinical trial report, subject data listings
1.116-1.118	ESPS2 Clinical Trials Report, ESPS2 protocol, amendments, IRB forms, sample case report forms, meeting notes, curriculum vitae
1.119-1.121	Randomization Scheme
1.121-1.138	Batch certificates, Audit certificates, statistical considerations, statistical analysis, computer-generated statistics and survival curves, Cox analysis, ANOVA
1.139-1.146	Excluded patients, Subject data listing, Summaries of case reports
1.147	Tables of Studies and Lists of Investigators

The following volumes were reviewed: 1.002, 1.003, and 1.077 through 1.109, 1.114 through 1.146.

Other amendments were also reviewed dated 1/19/99, 1/21/99, 1/25/99, 1/27/99 and 3/8/99. Electronic submission documents and files containing clinical information for ESPS2 were reviewed.

Table of Contents

Italics are used with a direct quote from the sponsor, Code of Federal Regulations, FDA guidelines, or from the literature. References are provided.

Background

The magnitude of stroke is measured in public health terms by stroke-specific incidence, prevalence, and mortality. [1] Stroke is the third commonest cause of mortality and a major cause of long-term morbidity. Thrombotic vascular disease is the most frequent cause of cerebrovascular disease in North America. Thrombotic stroke accounts for approximately 70-80% of all strokes with intracerebral hemorrhage accounting for approximately 10-30%.

Risk factors for stroke in order of decreasing importance include age, hypertension, cardiac disease, diabetes, cigarette smoke, hypercholesterolemia, and alcohol abuse. The strongest risk factor for stroke is age. The incidence rises exponentially with age with the majority of strokes occurring in patients over 65. Stroke risk is greater among men than women. African-Americans are more likely to suffer stroke than other ethnic groups. Modifiable risk factors for strokes include hypertension, cardiac disease (particularly atrial fibrillation), hypercholesterolemia, cigarette use, and alcohol abuse.

The second most powerful risk factor for stroke is hypertension. With the risk rising proportionately with increasing blood pressure (systolic or diastolic). Elevated blood pressure accelerates the progression of atheroselerosis and predisposes to small-vessel disease.

Cardiac disease is a significant risk factor particularly in patients with arrhythmias, valvular heart disease, coronary heart disease, and EKG evidence of left ventricular hypertrophy. Atrial fibrillation was associated with a five-fold increased risk of stroke in the Framingham study. Stroke risk is nearly double in those with antecedent coronary artery disease and nearly quadruples in those with cardiac failure. Diabetes is associated with an increased risk of stroke for both men and women. *The degree and progression of carotid atherosclerosis are directly related to cholesterol and LDL and inversely related to HDL.* [1]

Transient Ischemic Attacks (TIA) are a strong indicator of subsequent stroke. The annual risk ranges from 1 to 15%. The greatest risk of stroke occurs the first year after a TIA. Fewer than 20% of stroke patients with cerebral infarction will have a precedent TIA.

The mortality associated with stroke is greatest in the first thirty days with the rate ranging from 8 to 20%. Initial predictors at the onset of stroke of early mortality include impaired consciousness, severity of the initial clinical syndrome, hyperglycemia, and age. Survivors of stroke have 3 to 5 times the increased risk of death compared to the general population. The annual estimates of risk of death are 5-8% for stroke.

The risk of recurrent stroke is greatest in the first 30 days following the initial event. The risk is estimated to range from 3 to 10%. Long term stroke recurrence rates range in different studies from 4-14%/year. Risk factors for recurrence are valvular disease, congestive heart failure, and atrial fibrillation.

The treatment of TIA and ischemic stroke includes antiplatelet drugs such as aspirin and ticlopidine.

The sponsor has submitted an NDA for Aggrenox™, a combination product of dipyridamole (DP) and aspirin (ASA), to "

" The product is an extended release formulation of dipyridamole combined with immediate release aspirin to be taken orally twice a day. Each capsule will contain DP 200mg and ASA 25 mg. The Agency requires that, as outlined in CFR 300.50 for combination products, "two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population...". The regulatory history of both drugs is germaine to a discussion of the submission.

The final rule for aspirin was published in the Federal Register on October 23, 1998. The final rule approved the use of aspirin to "*Reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli*"[2]. The dose of aspirin approved is 50-325 mg once a day[3].

The FDA approved dipyridamole on December 6, 1961. This approval was made prior to the KeFauver-Harris amendment of 1962, which required scientific proof of efficacy prior to approval. Prior to that amendment drugs were approved solely on the basis of safety. Persantine® tablets are only approved for one indication: " as an adjunct to coumarin anticoagulants in the prevention of postoperative thromboembolic complications of cardiac valve replacement". The recommended dose for this indication is 75-100 mg four times a day. Persantine®

tablets are an immediate release formulation. The dipyridamole used in this application is an extended release capsule form that is not currently approved in the United States.
The combined product is approved and marketed in Europe and Africa. For a complete listing please see the Approved Marketing section of this review.

Description of Study Drug

Aggrenox™ is a combination antiplatelet agent developed for oral administration. Each contains an extended release form of 200-mg dipyridamole and 25-mg aspirin in an

TABLE 3.4.3.2:1 AGGRENOX™ capsules Qualitative and Quantitative Composition

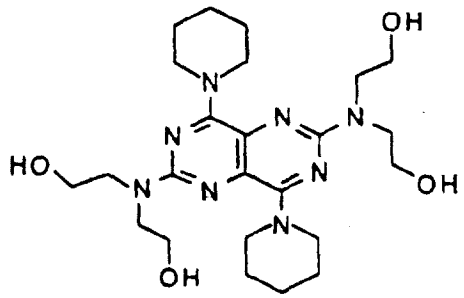
Ingredients	
ASA (aspirin)	
Corn Starch •	
Colloidal Silicon Dioxide •	
Aluminum Stearate •	
Lactose Monohydrate •	
Microcrystalline Cellulose •	
Sucrose •	
Titanium Dioxide •	
Acacia •	
Dipyridamole	
Tartaric Acid	
Hydroxypropyl Methylcellulose	
Dimethicone	
Talc	
Povidone	
Methacrylic Acid Copolyme	
Hydroxypropyl Methylcellulose Phthalate	
Triacetin •	
Stearic Acid •	
Total	
Capsule Shell**	

** Consisting of gelatin, water, titanium dioxide, red iron oxide, yellow iron oxide

Chemistry

Dipyridamole

The chemical composition is 2,6-bis(diethanolamino)-4,8-dipiperidino-pyrimido(5,4-d) pyrimidine and is shown below.

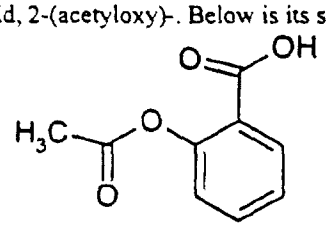


$C_{24}H_{40}N_8O_4$ *Mol. Wt. 504.63*

Dipyridamole is an odorless yellow, crystalline substance with a bitter taste. It is soluble in dilute acids, methanol, chloroform, and practically insoluble in water.

Aspirin

The chemical composition is benzoic acid, 2-(acetyloxy)-. Below is its structural formula.



$C_9H_8O_4$ Mol. Wt. 180.16

Aspirin is an odorless white, needle-like crystalline or powdery substance. When exposed to air it hydrolyzes into salicylic and acetic acids. Aspirin is highly lipid soluble and slightly soluble in water.

Manufacturing

A more in depth review of Aggrenox™ and its component drug substances can be found in the FDA Chemistry Review.

Preclinical Pharmacology and Toxicology Information

This application includes multiple studies involving animals. Below I have summarized the major findings by the sponsor. The sponsor repeatedly uses or makes references to drug products, which are not the formulation planned for market. Below is a table with the names and dosages of the major components for each product. The different formulations are important in the history of the development of Aggrenox™. Most of the preclinical trials were conducted using DP:ASA ratios for the earlier drug products. Most of the preclinical studies were conducted using a dipyridamole:aspirin ratio of 1:4-6. Unless otherwise noted these ratios were the ones tested. ~~The planned product for marketing is a dipyridamole:aspirin ratio~~ of 8:1. A substitution of the results obtained with one product (e.g. Persantine ER) cannot be made for Aggrenox™.

Product Names/Definitions

Name	Form	Dosage-Dipyridamole	Dosage-Aspirin	Total daily dose Aspirin	Total daily dose Dipyridamole
Asasantin®Extended Release / (Aggrenox™) /Aggrenox ER	Extended release BID	200 mg	25 mg	50 mg	400 mg
Asasantin®Immediate Release/	Immediate release TID	75 mg	330 mg	990 mg	225 mg
Persantin®Retard /Persantin-L	Extended release QD or BID	150-200mg	0 mg	0mg	150- 400 mg
Persantine ER	Extended release BID	150-200 mg	0 mg	0 mg	400 mg
Persantine Immediate Release®	TID or QID	75 mg	0 mg	0 mg	225 –300 mg

Reviewer's table

Adsorption, Distribution, Metabolism, and Excretion (ADME)

The summary application repeatedly refers to Persantine ER for the absorption, distribution, metabolism, and excretion of Aggrenox™. Persantine ER is the extended release form of dipyridamole without aspirin. Where pivotal pharmacokinetic and other studies are presented a comparison of Aggrenox™ with Persantine ER is always made. The FDA Pharmacology and Biopharmaceutics Reviews will be helpful in providing information on whether a substitution of Persantine ER information concerning ADME for Aggrenox™ is acceptable to the Agency. Persantine ER is not an approved product in the United States.

The sponsor states that the *pharmacokinetics of the individual components remain unchanged in the final product.* Dipyridamole peak plasma levels are reached 2-3 hours after administration with steady-state concentrations achieved within 3 days. Dipyridamole is metabolized predominantly in the liver by conjugation with glucuronic acid to form monoglucuronide. Dipyridamole is present in plasma 75-80% of the time as the parent compound and 20-25% as the monoglucuronide. Aspirin is converted to salicylates in the liver and has a plasma half-life of 15 minutes. Peak plasma levels of salicylic acid occur within 1-2 hours of dosing. Salicylates are predominantly excreted by hepatic metabolism with any unmetabolized salicylate excreted in the urine. Unmetabolized salicylate accounts for approximately 1-5% of the total salicylate.

Toxicology
Only one single dose study of DP/ASA in the 8:1 ratio was submitted. All other studies submitted used a ratio of 1:4-5. The single dose study with a DP:ASA ratio of 8:1 in rats suggested that the maximum non-lethal dose was 6750 mg/kg. Repeated dose, reproduction, mutagenicity, and carcinogenicity studies were performed using the reverse ratio of DP:ASA 1:4-5.
The sponsor found the target organs for toxicity were related to either the aspirin moiety or dipyridamole moiety. The changes noted are listed in the table below:

Pathologic Changes

Organ	Pathologic Changes
Gastrointestinal	Mucosal erosions and ulcers
Renal	Tubular atrophy and pelvic inflammation
Cardiovascular	Jet lesions and panarteritis

Reviewer's table

No repeated dose toxicity studies were performed in the planned product ratio.
Teratology studies suggested that the combination of dipyridamole and aspirin can produce embryotoxicity at maternally toxic doses. Further details may be found in the FDA pharmacology review of Aggrenox™.
Both mutagenicity and oncogenicity studies performed did not suggest carcinogenic potential.
No evidence of teratogenic potential or increased teratogenic effect for aspirin was suggested in studies with rats and rabbits.

The toxicities of these component drugs are well known. Aspirin is associated with the following adverse reactions:

1) Hematologic (e.g. prolongation of bleeding time)
2) GI side effects
3) Generalized symptoms
4) Cardiovascular
5) Central Nervous System
6) Fluid and Electrolyte
7) Hypersensitivity
8) Musculoskeletal
9) Metabolism
10) Reproductive
11) Respiratory
12) Special senses
13) Urogenital.

Dipyridamole is associated with the following adverse reactions:

1) Central Nervous System
2) Cardiovascular
3) Rash
4) Gastrointestinal
5) Constitutional.

Human Pharmacology

The antithrombotic action of Aggrenox™ may be the result of the additive antiplatelet effects of dipyridamole and aspirin.
Dipyridamole inhibits the uptake of adenosine into platelets, endothelial cells, and erythrocytes in a dose-dependent fashion. The inhibition results in an increase in local concentrations of adenosine, which act on the platelet A_2- receptor thereby stimulating platelet adenylate cyclase. This stimulation results in increased cyclic-

3',5'-adenosine monophosphate (cAMP) levels. Via this mechanism, platelet aggregation is inhibited which reduces platelet consumption. This mechanism is likely to be the major mechanism contributing for the antiplatelet effect. Dipyridamole also inhibits phosphodiesterase(PDE). Therapeutic levels of dipyridamole inhibit 3', 5'-guanosine monophosphate-PDE (cGMP-PDE). The inhibition of cGMP-PDE augments an increase in cGMP produced by endothelium-derived relaxing factor.
Aspirin irreversibly inhibits platelet cyclooxygenase thereby inhibiting production of Thromboxane A_2 (TXA_2). TXA_2 is a potent platelet activator and leads to aggregation. Aspirin effectively inhibits cyclooxygenase for the lifespan of the platelet since platelets lack a nucleus.

The sponsor has submitted a number of studies to provide pharmacokinetic data. The difficulty in the analysis of these studies lies in assumptions made about the relationship of Persantine ER to Aggrenox™, whether there are pharmacokinetic interactions between DP and ASA, and on the trial design. The FDA Pharmacology and Biopharmaceutics Reviews will provide greater detail on this issue.

The sponsor performed pharmacokinetic studies in healthy volunteers and 404 patients. The healthy volunteers received production and ESPS2 batches of Aggrenox™. The 404 patients were taken from the ESPS2 clinical trial. During the ESPS2 trial the formulation continued to undergo changes in composition. The ESPS2 trial collected information on pharmacokinetics as a means of assessing patient compliance. The trial was not strictly designed to obtain pharmacokinetics. The results from these trials are summarized in the tables below.

Selected Pharmacokinetic Studies for Aggrenox™ (all 4 tables below are from the sponsor)

PANEL 3.b.1.1 Table of Pharmacokinetic and Pharmacodynamic Studies

Clinical Study # (BI U#) Population Report Loc. (R) CRFs Loc. (C)	Design	Study Start/ Investigator(s)	Age Range/ Mean Age M/F	Treatment, Dose, Dosage Form, Duration	# of Subjects Rand. or/ Enrol./ (Completed)	Batch Number
Pivotal PK Studies						
IP 9.123 (U98-2379) healthy volunteers (R) (C) NAV	Randomized, open-label, multiple-dose, two-way crossover	1997/ J.G.W. Theis	18 - 55 33.2 [illegible]	Aggrenox ER 200/25 mg (production batch) b.i.d. x 4.5 days Aggrenox ER 200/25 mg (ESPS 2 batch) b.i.d. x 4.5 days	36 (33) 36 (34) Total: 36	710187 30104

Objective(s): Bioavailability of Aggrenox ER production batch compared to ESPS2 clinical batch

Other PK Information: Multiple-dose kinetics, achievement of steady-state, gender effects on DP, ASA, and SA pharmacokinetics.

Results: DP: The production batch was found to be bioequivalent to the ESPS 2 batch with respect to DP pharmacokinetics. Steady-state conditions were achieved within 48 hours for DP. AUC_{ss} was 3% lower in females than males, after correction for differences in body weight. ASA and SA: AUC_{ss} for ASA was increased by 19% in the production batch; however, the equivalence of AUC_{ss} for SA demonstrated that the production batch was equivalent to the ESPS 2 batch with respect to extent of absorption of ASA. The rate of absorption of ASA in the production batch was faster than the ESPS 2 batch (32% increase in $C_{max,ss}$ of ASA). However, since ASA produces its pharmacodynamic effect via irreversible acetylation of platelet cyclooxygenase, the time course of its pharmacodynamic activity is not dependent on pharmacokinetics but rather on the lifespan of the platelets (approximately 8-10 days). AUC_{ss} was 16% higher for ASA and 4% higher for SA in females compared to males, after correction for differences in body weight.

Note: The following abbreviations are applicable to this table:
ER=extended release; IR=immediate release; DP=dipyridamole, DP-Gluc=dipyridamole glucuronide; ASA=acetylsalicylic acid; PK=pharmacokinetic; SA=salicylic acid; NONMEM=non-linear mixed effects modeling; Lab=laboratory; IV=intravenous; SD=single dose; TIA=transient ischemic attack; N/A=not applicable; NAV=not available

Note: Number of subjects randomized (Rand.) is presented for randomized studies; number of subjects enrolled (Enrol.) is presented for nonrandomized studies; number of subjects completed (Completed) is included only for the pharmacokinetic and pharmacodynamic studies. Overall total represents total patients randomized or enrolled.

Note: A maximum of three investigators is listed for each study; "et al." indicates that a study had more than three investigators. A complete list of investigators and the studies in which they participated can be found in the List of Investigators.

Note: Results are presented for only those pharmacokinetic objectives that are relevant to this submission.

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12/14/98
[illegible]

Clinical Study # (BI U#) Population Report Loc. (R) CRFs Loc. (C)	Design	Study Start/ Investigator(s)	Age Range/ Mean Age M/F	Treatment, Dose, Dosage Form, Duration	# of Subjects Rand. or Enrol./ (Completed)	Batch Number
Pivotal PK Studies – continued.						
IP 9.70 (ESPS 2) (U96-0136) (U96-2194) (U96-2510) (U98-2750) TIA or stroke (R) (C)	Phase III, randomized, double-blind, placebo-controlled, multicenter, parallel	1988 Bailey, Banerjee, Baumgartner, et al.	19 - 97 66.7 3828 / 2774	Aggrenox ER (200 mg ER Persantine/ 25 mg IR ASA) b.i.d. x 2 years Persantine ER 200 mg capsule b.i.d. x 2 years IR ASA 25 mg b.i.d. x 2 years Placebo b.i.d. x 2 years	1650 1654 1649 1649 Total: 6602	[illegible]

Note: The total number of patients randomized excludes 438 patients at Center 2013, which was excluded due to scientific misconduct.

[a] Lot Numbers:
Aggrenox ER: 30104, 20102, 10405, 10307, 10103, 01002, 00719, 00619, 00507, 00302, 00103, 90611, 90502, 90308, 90206, 81010
Persantine ER 200mg: 30204, 20201, 10406, 10102, 01101, 00807, 00712, 00616, 00504, 00307, 00105, 90612, 90501, 90309, 90208, 81011, 10303
IR ASA: 30111, 11005, 10401, 10301, 10107, 01008, 00715, 00704, 00512, 00312, 00102, 90610, 90508, 90310, 90207, 81012
Placebo: 30210, 10904, 10402, 10302, 01207, 00709, 01010, 00610, 00411, 00215, 00101, 90609, 90417, 80912

Clinical Study # (IP U#) Population Report Loc. (R) CRFs Loc. (C)	Design	Study Start/ Investigator(s)	Age Range/ Mean Age M/F	Treatment, Dose, Dosage Form, Duration	# of Subjects Rand. or Enrol./ (Completed)	Batch Number
IP 9.70 (ESPS 2) (U96-0136) (U96-2194) (U96-2310) (U98-2750) (Continued)						
Objective(s): Single plasma DP and ASA concentration measurement, to monitor compliance. Other PK Information: Demographic effects (sex, age, weight) on PK of Persantine ER component, PK of Persantine ER component in target population; effect of renal function on DP pharmacokinetics; evaluation of potential for drug interaction between DP and ASA. Results: Plasma samples collected to evaluate compliance (N=247 for ASA, N=253 for Persantine ER, N=227 for Aggrenox ER, N=270 for placebo) were analyzed to determine DP, ASA, and SA pharmacokinetics in patients. DP and DP-Gluc: DP pharmacokinetics were not affected by concomitant administration of ASA. No differences were seen in DP pharmacokinetics in patients, compared to data obtained from studies in healthy volunteers (parameters in patients: volume of distribution of 159 L, $t_{1/2}$ of 9.92 and 10.8 hours in males and females, CL/F of 185 and 170 mL/min in males and females). DP and DP-Gluc clearance decreased with increasing age and increased with increasing weight. Population PK analysis showed that CL/F of DP was 40% lower in elderly (>65 years) compared to younger patients (<55 years), and was 15-20% lower in lighter (<67 kg) compared to heavier (>78 kg) patients. This agreed with results from an empirical analysis, which showed a 29% decrease in apparent clearance in elderly compared to young patients (>65 years compared to <55 years), and 14% decrease in lighter compared to heavier patients (<67 kg compared to >78 kg). Only a small difference (8% decrease) was found in DP apparent clearance and no difference was found in DP-Gluc apparent clearance in females compared to males, after correction for age and weight differences. There was no impact of renal function on DP and DP-Gluc concentrations. ASA and SA: ASA kinetics were not determined because a large number of samples were below detection limits. SA concentrations in elderly (>65 yrs) were 17% higher than in younger patients (<55 yrs). Plasma concentrations also increased with decreasing weight (19% higher in patients <67 kg compared to patients >78 kg). There were no differences between males and females, after correction for age and weight differences. While peak SA concentrations were achieved later in patients compared to healthy volunteers, the magnitude and shape of the plasma concentration-time profile was similar to that seen in healthy subjects. SA pharmacokinetics were not affected by concomitant administration of DP.						

Clinical Study # (IP U#) Population Report Loc. (R) CRFs Loc. (C)	Design	Study Start/ Investigator(s)	Age Range/ Mean Age M/F	Treatment, Dose, Dosage Form, Duration	# of Subjects Rand. or Enrol./ (Completed)	Batch Number
Pivotal PK Studies – continued						
IP 9.69 (U89-0187) healthy volunteers (R) (C) N/A	Randomized, double-blind, multiple dose, three-way crossover	1988/ C.A.P.F. Su	21 – 46 3 3 6 / 6	Persantine ER 200 mg b.i.d. x 3 days Aggrenox ER (200 mg ER Persantine/25 mg IR ASA) b.i.d. x 3 days IR ASA 25 mg b.i.d. x 3 days	12 (12) 12 (12) 12 (12) Total: 12	R0534 R0533 7010-1
Objective(s): Evaluation of potential for pharmacokinetic interaction between the Persantine ER and IR ASA components of Aggrenox ER. Other PK Information: Effect of gender on ASA pharmacokinetics. Results: DP: The bioavailability of DP was essentially unchanged on concomitant administration of DP and ASA (8% and 12% increase in AUC_{ss} and $C_{max,ss}$, respectively, for Aggrenox ER compared to Persantine ER). ASA and SA: The extent of absorption (AUC_{ss}) of ASA was not significantly affected (8% increase), but the rate of absorption of ASA was somewhat slower following administration of Aggrenox ER compared to administration of IR ASA alone, as evidenced by the 29% decrease in $C_{max,ss}$. However, since ASA produces its pharmacodynamic effect via irreversible acetylation of platelet cyclooxygenase, the time course of its pharmacodynamic activity is not dependent on pharmacokinetics but rather on the lifespan of the platelets (approximately 8-10 days). No significant changes were observed in SA kinetics. No significant differences were observed in AUC_{ss} for ASA and SA between males and females, after correction for differences in body weight.						

Additional trials with Persantine ER were presented in summary format. Selected results obtained from these trials include:

IP 9.123

1) *AUC_{ss} for ASA was increased 19% in the production batch, however, the equivalence of AUC_{ss} for SA demonstrated that the production batch was equivalent to the ESPS2 batch with respect to extent of absorption of ASA*

ESPS2

2) The sponsor notes that *ASA kinetics were not determined because a large number of samples were below detection limits.*
3) *DP clearance decreased with increasing age and increased with increasing weight.*
4) *SA concentrations in the elderly (>65yrs) were 17% higher than in younger patients (< 55 yrs).*
5) *SA plasma concentrations also increased with decreasing weight.*
6) *Peak SA concentrations were achieved later in patients compared to healthy volunteers.*

IP 9.69

7) *Rate of absorption of ASA was somewhat slower following administration of Aggrenox ER compared to the administration of IR ASA alone.*

The extrapolation of data from healthy volunteers to patients is not easily performed. The mean age in the healthy volunteers was 33.2 years for IP 9.123 and was 33.6 years for IP.9.69.. The mean age in the ESPS2 trial was 66.7 years. Elderly patients take other medications, have other medical conditions, and reduced creatinine clearance, which could effect DP clearance and ASA clearance. ESPS2 did not determine ASA kinetics and was a clinical trial, which assessed efficacy, safety, and compliance.

The sponsor states:

1) With coadministration of DP and ASA as Aggrenox™ ER, a small increase in AUC (8%) and C_{max} (12%) was noted in DP pharmacokinetics on average
2) only a small increase (8%) was noted in the AUC of ASA, but a 29% decrease was observed in C_{max} following administration of Aggrenox™ ER, compared to the administration of ASA alone. However, since ASA produces its pharmacodynamic effect via the irreversible acetylation of platelets, the time course of its pharmacodynamic activity is not dependent on the pharmacokinetics of ASA but rather on the lifespan of the platelets (approximately 8-10 days).
3) The small difference observed in the pharmacokinetics of SA following coadministration of DP and ASA is biologically irrelevant.
4) 200 mg Persantine extended release + 25 mg ASA as immediate release tablet given b.i.d. represent the optimal dosage forms and doses, as dynamics of the individual components are maintained and the overall effect of the combination is superior due to the additive effects which could not be achieved by any dose of the individual components.

The sponsor attempts to explain any discrepancies in pharmacokinetic data by the pharmacodynamic effect. The sponsor's PK data demonstrate the AUC of aspirin alone, following a 25 mg oral dose, to be greater than the AUC for the same dose of aspirin in the combination product. The effect of this difference is unclear at this point. There were no dose finding studies performed in patients to determine optimal dose of aspirin and optimal dose of dipyridamole used in this fixed combination product.

Clinical Studies Summary

The tables below are brief synopses of the major trials to be discussed.

Pivotal Clinical Trial

Trial	Trial type	No. subjects	Treatments	Results
ESPS-2	International, Multicenter, randomized, parallel group, double-blind, placebo-controlled, 2 by 2 factorial design	6602 patients who experienced a TIA or stroke within 3 months prior to study entry from 59 centers in 13 countries	1)Placebo, 2) aspirin 25 mg po bid, 3) extended release dipyridamole 200 mg po bid, 4) Asasantin®Extended Release/Aggrenox™ (extended release dipyridamole 200 mg + aspirin 25 mg po bid)	Organized and analyzed on an intent to treat basis, demonstrated a reduction in the secondary prevention of stroke, and a reduction in the combined endpoint of stroke and/or death but did not affect the endpoint of death (see efficacy section for greater details)

Reviewer's table

Clinical Trials in Support of the application

Trial	Trial type	No. subjects	Treatments	Results
ESPS-1	International, Multicenter, randomized, parallel group, double-blind, placebo-controlled	2500 patients who experienced a TIA or stroke within 3 months prior to study entry from 16 centers in 6 countries	1) Placebo, 2)Asasantin® Immediate Release	Primary efficacy – endpoint of stroke and/or death Results at 24 months, Primary endpoint of stroke or death reached by 22.6% placebo patients and 15.2% Asasantin® Immediate Release patients
U88-0473	Single center, Randomized	137 patients who had experienced TIA or Reversible Ischemic Neurologic Deficit (RIND)	1)Dicumarol ± heparin 2) ASA 330mg po tid + Persantine Immediate Release (DP 75 mg) po tid ± heparin	Trend towards lower incidence of recurrent TIA, RIND, or lower occurrence of stroke in both groups, unpublished work presented at the World Congress of Neurology 1981

Reviewer's table

For these European studies, a slight difference in the definition of stroke must be mentioned. Stroke in Europe includes TIA in its definition. TIA is a form of minor stroke.

Description of Protocol

Title: ESPS 2 Second European Stroke Prevention Study

A) **Objective:** The aim was *to investigate the effect of dipyridamole and of low dose ASA used alone or in combination, a placebo group providing the baseline, in the prevention of stroke and of death in patients who have already suffered from recent minor or major cerebrovascular accidents of ischaemic origin.*

B) **Study Design:** This trial was an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group with a two by two factorial design. The trial was organized and planned to be analyzed on intent to treat basis.

C) **Subjects:** The trial was designed initially to include 5000 patients with 1250 in each of the four treatment groups. After an interim analysis the sample size was increased from 5000 to 7000 patients.

D) **Disease definitions:**

1) *TIAs : a focal disturbance of the cerebral circulation which results in a clinical neurological deficit recovering within twenty-four hours without functional impairment at standard clinical neurological examination.*

2) *Stroke : a focal disturbance of the cerebral circulation which results in a functional neurological deficit lasting more than 24hours.*

For the purpose of this study, strokes may be classified into minor strokes or major strokes according to modified Rankin scale :

a) *Minor strokes are CVA in which the functional neurological deficit either disappears after more than 24 hours or if there are residual symptoms, they do not impede severely the patient's lifestyle, involving only a minor handicap.*

In a minor handicap, symptoms lead to some restriction of lifestyle, but do not interfere with the patient's capacity to look after himself (grades 0, 1, 2).

b) *Major strokes are CVA in which the functional neurological deficit impedes the patient's lifestyle, involving a moderate or more severe handicap.*

1) *Moderate handicap : symptoms which significantly restrict lifestyle and/or prevent totally independent existence.*

2) *Moderately severe handicap : symptoms which clearly prevent independent existence though not needing constant attention.*

3) *Severe handicap: totally dependent, requiring constant attention day and night (grades 3, 4, 5).*

Therefore, the diagnosis of ischaemic cerebrovascular accident will be based on clinical symptoms.

E) Inclusion Criteria

Adult patients (i. e. over 18 years of age)

1) *-suffering from a recent CVA;*
2) *-whose CVA occurred within 3 previous months*
3) *-after sufficient clinical stabilization of their neurological and general condition after a stroke.*

F) Exclusion criteria

Diagnosis

1) *Cerebral haemorrhage*
2) *Brain tumor*
3) *Cerebral disorders related to the following diseases :*
   Syncope, drop attacks, migraine;
   Congenital vascular malformation: aneurysm, angioma
   Should not be included, unless the occurrence of a recent CVA (not older than 3 months) is proven by CT scan.

History of

4) *allergy to aspirin*
5) *active peptic ulceration*
6) *neurovascular surgery 6 weeks prior to inclusion.*

General condition

7) *dysphagia*
8) *unconsciousness or dementia*
9) *unreliable patients who, in the opinion of the trialist, would be unsuitable for inclusion in the study due to their inability, unreliability or non-cooperation (psychotic patients, patients with poor memory, patients in unsuitable social situation)*

Concomitant diseases

10) *Bleeding disturbances*
11) *Unstabilized hypertension with significant risk of hypertensive encephalopathy*
12) *Chronic renal failure*
13) *Poor life expectancy, life-threatening disease (neoplasia, liver cirrhosis, etc.)*
14) *Uncontrolled diabetes*
15) *Conditions for which anticoagulation is necessary*

Concomitant treatment

16) *Nonsteriodal anti-inflammatory agents, anti-coagulants or anti-platelet agents including ASA and dipyridamole which cannot be changed to a suitable alternative medication.*

Others

17) *pregnancy*
18) *Refusal : from patient's own decision or in accordance with family wishes (aphasia) and/or his general practitioner.*

G) Treatment Assignment

Patients were allocated according to a minimization technique, which took into account the initial diagnosis (TIA or stroke), sex, age, and study center, by European Organisation for Research and Treatment of Cancer (EORTC). Below is a table of the four arms of the trial.

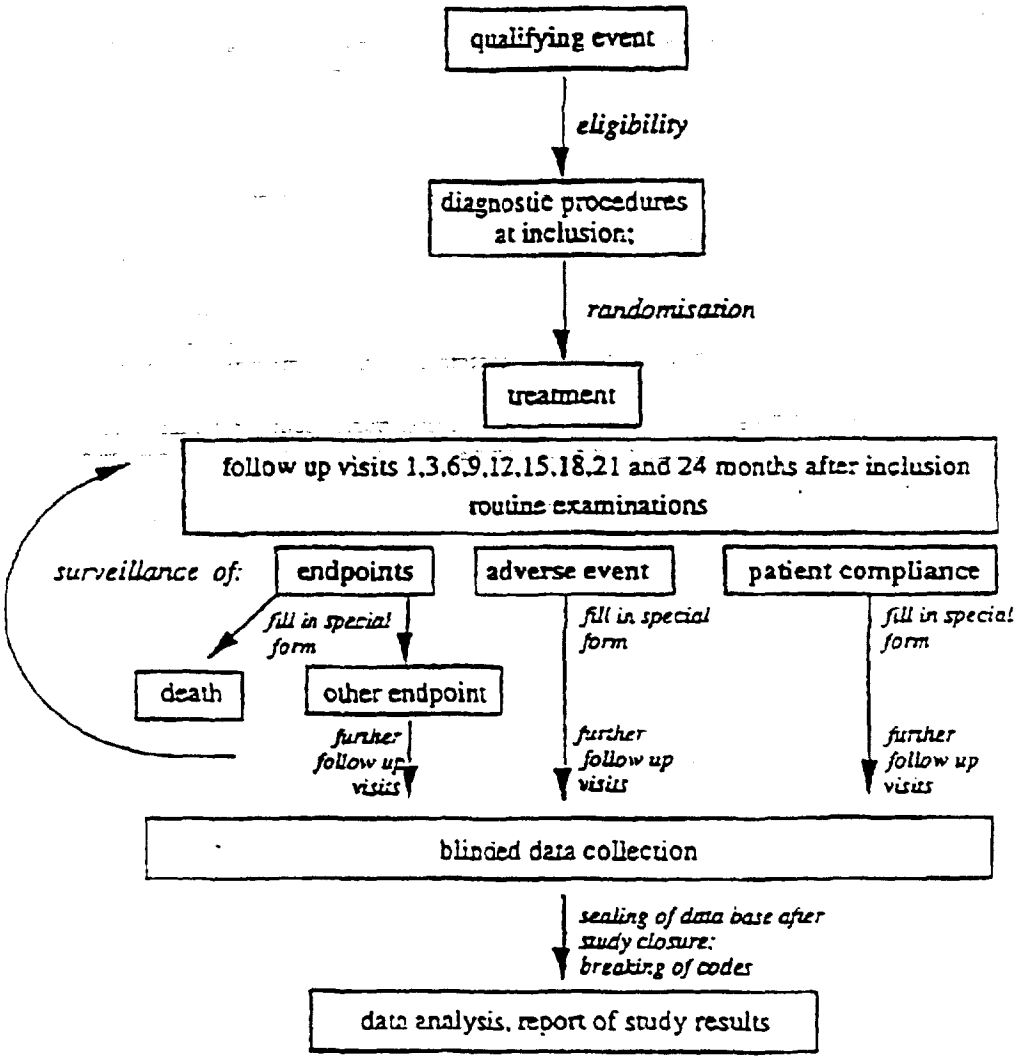
Treatment and Dose Regimen

Group	Aspirin dose	Dipyridamole
Placebo	None	None
ASA	25 mg po bid	None
DP	None	200 mg po bid (slow release)
DP + ASA	25 mg po bid	200 mg po bid (slow release)

Reviewer's table

H) Flow of Trial

Sponsor's diagram from Clinical Trials Report



Various levels of quality control have not been indicated in this diagram for the sake of simplicity.

I) Follow-up

Each patient would receive study drug and be followed for 24 months unless a fatal event occurs. Follow-up continued regardless of whether an end-point or relevant event was reached or whether treatment was continued or not. Follow-up visits were scheduled: at the end of months 1,3,6,9,12,15,18,21,24 after inclusion. The planned analysis would take into account events occurring within the 24 months.

J) End-point Occurrence

Special forms were filled out for stroke or death.

For stroke the following information was collected if possible:

1) date of onset and description of symptoms
2) location

3) severity (modified Rankin scale)
4) fatal outcome
5) time for recovery
6) CT scan
7) other examinations as necessary.

For death the following information was collected if possible:

1) date and circumstances of death
2) symptoms, description, date of onset, location in case of death due to stroke or myocardial infarction (MI)
3) autopsy confirming or defining the cause.

K) Evaluations

1) Diagnosis prior to inclusion

Prior to inclusion the diagnosis of CVA must be assessed by:

a) *-clinical neurological examination for:*
-neurological signs
-date of event
-stabilization of the clinical status

b) *-CT scan: a CT scan is strongly recommended in view to confirm the thrombotic origin of the vascular accident and to exclude other possible causes such as tumors or cerebral haemorrhages.*

CT scan should be performed at earliest 3 days after the CVA, at the latest before inclusion (3rd month).

(A negative scan is not a reason for non inclusion if clinical signs are or were clear enough to state the diagnosis of CVA).

c) *- checking of exclusion criteria as listed above.*

2) *At entry*

At entry, patients will undergo clinical and neurological examination, ancillary examinations and biological measurement.

A) The clinical examination included:
1) vital signs,
2) past medical history,
3) present medical history,
4) social habits (smoking, alcohol use, and coffee consumption).

B) The neurological examination recorded:
1) date of qualifying event,
2) history of previous CVA,
3) Location and arterial site involved,
4) Importance and description of residual impairment.

C) The ancillary examinations included:
1) ECG (mandatory)
2) CT scan (strongly recommended)
3) Isotopes-brain scan
4) Cerebral angiography
5) Doppler
6) Nuclear Magnetic Resonance
7) E.E.G.
8) Chest X-ray.

D) The biological measurements were performed at 0, 12, and 24 months and included:
1) complete blood count,
2) blood urea
3) cholesterol
4) uric acid
5) liver function tests.

E) The follow-up visits assessed intercurrent end-points or relevant events, side effects, and compliance in addition to the above listed items. Specific safety information was assessed. Special attention was paid to occurrence of hemorrhage, gastrointestinal complaints, headaches, and any other unusual complaints.

L) Endpoints (per the original protocol)

Primary end-points were:

1) Strokes

The first stroke (fatal or not) occurring after inclusion within 2 years will be taken into account. Fatal stroke is defined as a stroke followed by death, if there is a clear-cut relation between stroke and death. Death may be either directly related to the stroke or to a complication.

2) Total mortality

Total mortality (including fatal strokes) of any cause occurring within 2 years (it can occur after a non-fatal end-point or a relevant event).

Secondary end-points were:

1) TIAs
2) Acute myocardial infarction

The first acute myocardial infarction, occurring within 2 years (either fatal or not) will be taken into account. A fatal myocardial infarction is defined as a myocardial infarction followed by death. Death may be directly related to the myocardial infarction or to a complication.

3) Ischemic events

Ischaemic events, supposedly of thrombotic origin, are a combination of the following end-points or events:

Strokes
Acute myocardial infarction
Sudden death

which will be analysed together.

A sudden death is a death occurring within 24 hours after the onset of symptoms, the aetiology of which cannot be defined: poor symptomatology and no autopsy.

Other vascular events will also be checked: lung embolism, deep venous thrombosis, obstruction of peripheral arteries, retinal vascular accidents.

M) Compliance assessment

Compliance was assessed at each visit by interview and pill count. Serum analysis for aspirin and dipyridamole levels was performed twice during the study period; however, this analysis was not performed for all patients.

N) Statistical Analysis

Four treatment groups were planned with 1250 patients in each group. The number was computed to generate *80% power with a type I error of ≤ 0.05 in view to detect a difference of 33% risk reduction.* The statistical analysis was performed on an intent to treat basis. The major end-points were to be studied by survival analysis using the Gehan's test. The comparison of survival was to be performed between the four groups and pooled group analysis. The Cox model was planned to assess the potential effects of covariates.

An interim analysis was planned three years after the beginning of the study or when 1600 patients had reached two years of follow-up.

O) Trial Organization

Committees included:

1) Steering Committee
2) Ethics Committee
3) Protocol and Publishing Committee
4) Coordination Committee
5) Morbidity and Mortality Assessment Group (MMAG)
6) Statistical Center.

P) Amendments

No major protocol amendments were carried out during the study.

After recruitment was stopped, the investigators were able to withdraw patients with non-rheumatic atrial fibrillation, after several publications demonstrated benefit of vitamin K antagonist therapy in similar patients. After an interim analysis the Steering Committee recommended the increase in sample size.

Results of Pivotal Efficacy Trial: ESPS2

A clinical data summary and statistical analysis for this trial is contained in NDA vols. 1.003. The study report and protocol are contained in vol 1.116.
This trial was carried out from February 1989 to March 1995 involved 60 centers in 13 countries in Europe. Investigators and their sites are listed below.

Belgium

University of Antwerp, General Hospital Middelheim, Dept of Neurology, Antwerp. *Main Investigator :* DE DEYN PP, MD,Ph.D, MMPR.

Cliniques Universitaires Saint-Luc, Dept of Neurology, Brussels. *Main Investigator :* LATERRE C, MD, PhD.

U.Z. Gasthuisberg, Dept of Neurology, Leuven. *Main Investigator :* CARTON H, MD,Ph.D.

CHU, Dept of Neurology, Liège. *Main Investigator :* FRANCK G, MD, PhD.

Finland

University Hospital of Kuopio, Dept of Neurology, Kuopio. *Main Investigators :* RIEKKINEN PJ, MD, PhD, SIVENIUS J, MD, PhD.

Savonlinna Central Hospital, Dept of Neurology, Savonlinna. *Main Investigator :* KILPELAINEN H, MD.

University Hospital of Turku, Dept of Neurology, Turku. *Main Investigator :* RINNE UK, MD.

France

Centre Gui de Chauliac, Dept of Neurology A, Montpellier. *Main Investigator :* BLARD JM, MD.

Marseille CHU Timone, Dept of Neurology, Marseille. *Main Investigator :* KHALIL R, MD.

Germany

Kliniken Schnarrenberg, Dept of Neurology, Tübingen. *Main Investigator :* DICHGANS J, MD.

Fachklinik Rhein/Ruhr, Dept of Neurology, Essen. *Main Investigator :* SCHÜTT P, MD, KOLEN M, MD.

University of Essen, Universitätsklinik, Dept of Neurology, Essen. *Main Investigator :* DIENER HC, MD.

Albertinen-Haus Hamburg, Medizinisch-Geriatrische Klinik, Dept of Neurology, Hamburg. *Main Investigator :* MEIER-BAUMGARTNER HP, PD, DR.

Kliniken St. Antonius, Medizinische Klinik, Dept of Neurology, Velbert. *Main Investigator :* FÜSGEN I, MD.

University Hospital Mainz, Dept of Neurology, Mainz. *Main Investigator :* KRAEMER G, MD.

Diakoniekrankenhaus Rotenburg (Wümme), Dept of Neurology, Rotenburg (Wümme). *Main Investigator :* HAGENAH R, MD.

Nordwest-Krankenhaus Sanderbusch, Dept of Neurology, Sande. *Main Investigator :* ROHKAMM R, MD.

Klinikum Minden, Neurologische Klinik, Dept of Neurology, Minden. *Main Investigator :* BUSSE O, MD.

Ireland

Cork University Hospital, Dept of Neurology, Cork. *Main Investigator :* GALVIN R, MD, MRCP.

University College Hospital, Dept of Neurology, Galway. *Main Investigator :* MORAN J, MA, MB, FRCP.

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Prot. Ziekenhuis 'Willem Alexander', Dept of Neurology, 'S Hertogenbosch. *Main Investigator :* PEPERKAMP JPC, MD.
Elisabeth Ziekenhuis, Dept of Neurology, Venray. *Main Investigator :* WIEZER HA, MD.

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Hospitais da Universidade de Coimbra, Dept of Neurology, Coimbra. *Main Investigator :* CUNHA L, MD.
Hospital Geral Santo Antonio, Dept of Neurology, Porto. *Main Investigator :* CASTRO LOPES J, MD.

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Hospital General C.S. Vall d'Hebron, Dept of Neurology, Barcelona. *Main Investigator :* MOLINS M, Ph.D.
University Hospital San Juan, Hospital Clinic Alicante, Dept of Neurology, San Juan - Alicante. *Main Investigator :* MATIAS GUIU, M.D.
Hospital La Fe, Dept of Neurology, Valencia. *Main Investigator :* YAYA R, MD.

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Karolinska Hospital, Dept of Neurology, Stockholm. *Main Investigator :* WAHLGREN NG, MD.

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Regionsjukhuset Örebro, Dept of Neurology, Örebro. *Main Investigator :* NILSSON A, MD.

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Hôpital Cantonal de Genève, Dept of Internal Medicine, Geneva. *Main Investigator :* WALDVOGEL F, MD.

United Kingdom
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St. Woolos Hospital, Dept of Neurology, Newport. *Main Investigator :* BROWNE SEM, MRCP.
Derbyshire Royal Infirmary, Dept of Medicine for the Elderly, Derby. *Main Investigator :* MISHRA RM, MBBS, FRCPI.
Oldchurch Hospital, Neurology Research, Romford. *Main Investigator :* CAPILDEO R, FRCP, MBBS.
Orsett Hospital, Neurology Office, Orsett Grays. *Main Investigator :* CAPILDEO R, FRCP.
Bristol General Hospital, Dept of Neurology, Bristol. *Main Investigator :* WINDSOR ACM, MD.
Norfolk & Norwich Health Care Nastrust, Dept of Medicine for the Elderly, Norwich. *Main Investigator :* FULCHER R, MB, BcH, BAO, MRCPI.
Royal Infirmary, University Dept of Medicine, Glasgow. *Main Investigator :* LOWE G, MD, FRCP.
Jersey General Hospital, Dept of Neurology, St. Helier. *Main Investigator :* RICHARDSON MR, BSc (Med.Sci.), MBChB, MRCP (UK).
Crawley Hospital, Dept of Neurology, Crawley. *Main Investigator :* BAILEY R, MA, FRCP.
Bolton General Hospital, Dept of Neurology, Bolton. *Main Investigator :* BANERJEE AK, MD.
Leeds General Infirmary, Medical Unit, Leeds. *Main Investigator :* PRENTICE CRM, MD, FRCP.
Woodend Hospital, Dept of Medicine for the Elderly, Aberdeen. *Main Investigator :* HAMILTON SJC, FRCP (Glas.).
North Staffs Royal Infirmary, Dept of Neurology, Stoke-on-Trent. *Main Investigator :* SCARPELLO J, MD, FRCP.
Cardiff Royal Infirmary, Dept of Neurology, Cardiff. *Main Investigator :* WOODHOUSE K, MD, FRCP.

Sponsor's table from clinical trial report

Investigators' curriculum vitae, informed consent forms, and institutional board review approval information are provided in vol. 118.

A) Patient Enrollment and Disposition
A total of 7054 randomization numbers were issued. A total of fourteen numbers were issued to several centers, which were not used. *Patients were randomised to treatment groups according to the minimisation technique which took into account the initial diagnosis (TIA or stroke), sex, age and study center.* The allocation/randomization scheme is found in vol. 1.119, 1.120, and 1.121.
The scheme distributed treatments at sites so that a balance was achieved between all four treatments at each center. No country contributed more than 23% of the patients. Below is a table of the distribution of country of origin for patients. The largest center was University Hospital of Kuopio in Finland (center 2411) which contributed 682 patients (9.7%). The next three largest sites were Univerisdade de Coimbra in Portugal (center 2212) which contributed 453 patients (6.4%), St. Ignatius Ziekenhaus in the Netherlands (center 2011) which contributed 451 patients (6.4%), and Streekziekenhuis Almelo in the Netherlands (center 2013) which contributed 438 patients (6.2%).

TABLE 8.3.1: 3. COUNTRY OF ORIGIN OF PATIENTS INCLUDED IN ESPS 2
Source data: appendix 15.9.2.StAn.2: Demographic and Baseline Data

	Country	Number of patients	% of total
1	Norway	259	3.9
2	Sweden	459	7.0
3	Finland	947	14.3
4	Belgium	379	5.7
5	Switzerland	14	0.2
6	Germany	434	6.6
7	France	89	1.3
8	Netherlands	1509	22.9
9	Spain	292	4.4
10	Italy	134	2.0
11	Portugal	649	9.8
12	United Kingdom	1367	20.7
13	Ireland	70	1.1
1-3	*Scandinavia*	*1665*	*25.2*
4-8	*Northwestern Europe*	*2425*	*36.7*
9-11	*Southern Europe*	*1075*	*16.3*
12-13	*UK & Ireland*	*1437*	*21.8*
	Total	6602	100.0

Sponsor's table

B) Disposition

Below is a table with the disposition of patients during the trial. There was one center that was excluded from the trial.
An audit of center 2013 suggested scientific misconduct at that site so the center was excluded from the efficacy analysis. A complete explanation of the misconduct is provided later under the section labeled Center 2013. Therefore the sponsor's analysis was based on the 6602 reliable patients. Retrospectively another 138 patients were not eligible for the study because of misdiagnosis (n=44) and ineligible later because of inclusion/exclusion criteria (n=94). These 138 patients were included in the intention-to-treat analysis. The patient's data from center 2013 was considered so unreliable it was not included in any safety analysis.

ESPS2: Disposition of patients (Randomized patients)

	TOTAL	Placebo	ASA	DP	DP+ASA
Randomized	7054	1764	1762	1765	1763
Excluded (Center 2013 and 14 erroneous entries)	452	115	113	111	113
Included for final analysis	6602	1649	1649	1654	1650
Misinclusions /Misdiagnosis	138	28	37	31	42
Completed study: reached 24 months	3871/6602 (58.6%)	980/1649 (59.4%)	1023/1649 (62%)	923/1654 (55.8%)	945/1650 (57.3%)
Completed study: treated until death	392/6602 (5.9%)	108/1649 (6.5%)	102/1649 (6.2%)	100/1654 (6%)	82/1650 (5%)
Lost to follow up for Stroke (Before special investigation)	108	31	11	28	38
Lost to follow up for Stroke (After special investigation)	28	10	6	6	6
Lost to follow up for Death (Before special investigation)	44	14	8	16	6
Lost to follow up for Death (After special investigation)	15	7	4	2	2
Ceased Treatment	2339/6602 (35.4%)	561/1649 (34%)	524/1649 (31.8%)	631/1654 (38.1%)	623/1650 (37.8%)
Reason for Treatment cessation: adverse event	1698/6602 (25.7%)	390/1649 (23.7%)	328/1649 (23.2%)	467/1654 (28.2%)	459/1650 (27.8%)
Reason for Treatment cessation: non-medical	370/6602 (5.6%)	98/1649 (5.9%)	79/1649 (4.8%)	107/1654 (6.5%)	86/1650 (5.2%)
Reason for Treatment cessation: other	232/6602 (3.5%)	64/1649 (3.9%)	50/1649 (5%)	48/1654 (2.9%)	70/1650 (4.2%)
Reason for Treatment cessation: unknown	39	9	13	9	8

Reviewer's own table from sponsor's information

Less than 1% of the total number of subjects were lost to follow-up. The data handling rules for the NDA submission differed from that planned for the clinical trial report thus a special investigation was undertaken for patients lost to follow up.

A special investigation was performed of patients lost to follow-up for stroke or death. This investigation was performed after differences in the data handling rules were appreciated between the NDA requirements and the clinical trial report (CTR) for ESPS2. Below is a table with the differences in patient accounting between the NDA data handling rules and the CTR data handling rules prior to the special investigation. Each center investigator conducted the investigation for their lost to follow-up patients.

Differences in Data Handling Rules and Censoring Times for lost to follow-up patients

Event	NDA (number of patients)	CTR (number of patients)
Stroke	108	37
Death	44	42

Reviewer's table from sponsor's information

The sponsor wrote, *The investigators at each center remained blinded with respect to treatment group during the special investigation. The intended use of stroke information was in the worst-case and investigator-diagnosed stroke analyses only; the intended use of the new death information was in the worst-case patient survival analysis only. However, during the course of the investigation of the 108 patients lost to follow-up, it was discovered that four patients who had been considered alive at two years according to the NDA handling rules had actually died before that time. These four corrections were therefore added to the primary analyses of death. The primary analyses were not modified in any other way.*

Approximately twenty-five percent of patients discontinued for an adverse event. The term "other" under treatment cessation refers to those patients who moved, refused to participate, or whose general practitioner refused to participate.

Misdiagnosis/Misinclusions

PANEL 8.8.2.2.2:1 Summary of Misinclusions and Misdiagnoses
ESPS2 – Intent-to-Treat Population

	Treatment Group				
	DP 200 mg/ ASA 25 mg b.i.d. n (%)	DP 200 mg b.i.d. n (%)	ASA 25 mg b.i.d. n (%)	Placebo n (%)	Overall
Total Number of Patients	1650	1654	1649	1649	6602
Number of Patients Misincluded or Misdiagnosed as Determined by MMAG	42 (2.5%)	31 (1.9%)	37 (2.2%)	28 (1.7%)	138 (2.1%)
Misinclusion	27 (1.6%)	23 (1.4%)	26 (1.6%)	18 (1.1%)	94 (1.4%)
Misdiagnosis	15 (0.9%)	8 (0.5%)	11 (0.7%)	10 (0.6%)	44 (0.7%)
Types of Misinclusion or Misdiagnosis:					
Insufficient Argument for CVA	5 (0.3%)	1 (<0.1%)	4 (0.2%)	4 (0.2%)	14 (0.2%)
Qualifying Event >3 Months Before Inclusion	5 (0.3%)	5 (0.3%)	4 (0.2%)	4 (0.2%)	18 (0.3%)
Patients Clinical Condition Unstable	2 (0.1%)	1 (<0.1%)	3 (0.2%)	3 (0.2%)	9 (0.1%)
Cerebral Hemorrhage	2 (0.1%)	0	3 (0.2%)	1 (<0.1%)	6 (<0.1%)
Brain Tumor	4 (0.2%)	5 (0.3%)	6 (0.4%)	3 (0.2%)	18 (0.3%)
Nonspecific Cerebral Disorder and no CT-Scan or CT-Scan Normal	8 (0.5%)	3 (0.2%)	9 (0.5%)	4 (0.2%)	24 (0.4%)
Bleed Disturbances/Contraindication of ASA	2 (0.1%)	3 (0.2%)	0	1 (<0.1%)	6 (<0.1%)
Renal Failure with Serum Creatinine >221 umol/L	5 (0.3%)	7 (0.4%)	2 (0.1%)	2 (0.1%)	16 (0.2%)
Poor Prognosis	5 (0.3%)	2 (0.1%)	2 (0.1%)	1 (<0.1%)	10 (0.2%)
NSAID or Antiplatelet Indicated	2 (0.1%)	3 (0.2%)	2 (0.1%)	2 (0.1%)	9 (0.1%)
Anticoagulation Indicated	1 (<0.1%)	1 (<0.1%)	0	2 (0.1%)	4 (<0.1%)
Refused Consent	1 (<0.1%)	0	1 (<0.1%)	1 (<0.1%)	3 (<0.1%)
Unreliable Patient	0	0	1 (<0.1%)	0	1 (<0.1%)

Note DP = Dipyridamole; ASA = Acetylsalicylic acid; DP-ASA = AGGRENOX™; MMAG = Morbidity and Mortality Assessment Group; NSAID = Non-steroidal anti-inflammatory drug

Note Misinclusion is defined as ineligibility known before inclusion in trial; misdiagnosis is defined as ineligibility that became apparent after inclusion in trial.

Reference Table 1.2.0

These patients were distributed throughout all treatment groups. There was no obvious removal of "inappropriate patients" from one particular group.

Treatment Cessation

Below is a table with the details of treatment cessation from the clinical trial report provided by the sponsor. The patients listed below are the modified ITT population. The modified ITT population excluded patients from Center 2013 and the patients who were considered to have a misdiagnosis or misinclusion.

TABLE 10.2.4: 2. REASONS FOR TREATMENT CESSATION
Source data: appendix 15.9.2.StAn.5 : Safety Data

Type of Adverse Event:	Number or % of patients who stopped taking treatment				
	Placebo	ASA	DP	DP-ASA	Total
	Number of events:				
Reason for cessation:					
Any Reason:	360	366	485	479	1690
Medical:	275	290	385	398	1348
Non-Medical:	81	72	95	79	327
Adverse Event:	127	141	249	262	779
gastro-intestinal:	60	61	103	116	340
headache:	39	31	132	133	335
bleeding:	5	20	3	21	49

Sponsor's table

The major reason for treatment cessation is medical. Medical reasons for discontinuation of the treatment included adverse events. Below is a table of percent withdrawal due to adverse event.

Percentages of Patient withdrawal from Table 10.2.4: 2 above for any reason, medical reasons, and adverse event

Treatment Group	Any reason	Medical	Adverse Events
Placebo (n=1649)	21.8%	16.7%	7.7%
ASA (n=1649)	22.2%	17.6%	8.6%
DP (n=1654)	29.3%	23.3%	15.1%
DP+ASA (n=1650)	29%	24.1%	15.9%

Reviewer's table

Data missing in above table includes 4 patients in the placebo and ASA groups, 5 patients in the DP alone group, and 2 patients in the DP-ASA group. Bleeding complications were responsible for the excess treatment cessation in the ASA treated groups. Non-medical reasons included moving, patient refusal, general practitioner refusal, etc.

To assess the independence of the major endpoint analysis of the decision to exclude centre 2013 and the patients lost to follow up, endpoint data were reanalysed with the inclusion of centre 2013 and using the "worst case approach", assuming all patients that were lost to follow up had reached the endpoint.

Center 2013

After a series of events occurred which strongly suggested that scientific misconduct was occurring at center 2013, the ESPS 2 executive committee decided to exclude this center for the preservation of the scientific quality and integrity of the rest of the study.

Irregularities that initially aroused suspicion are.

1) recruitment of patients was very rapid (> 300 patients/yr.) despite one trialist at the center
2) follow up visits were perfectly regular and occurred when the trialist was away
3) follow up visits occurred on weekends and official non-working holidays
4) incidence of adverse events was lower than that from other centers
5) compliance of patients was better than in other centers
6) variability of data (pill counts, blood pressures) was too low for a clinical study
7) trialist declined open collaboration with both the central ESPS2 study organization as a committee member and with the local clinical monitor
8) Frequently there were a posteriori corrections of the dates of the ECG records and these dates correlated better with other baseline data from the same patients.

The Steering Committee recommended in 1992 that an independent observer audit the center. The audit performed in January 1993 observed the trialist delegated the responsibility of seeing patients to one of his colleagues who was not associated with the trial. In June 1993 the expert laboratory for plasma DP and salicylic acid (SA) concentration determinations from center 2013 were strikingly different from those collected at other sites.

DP and SA were both present in all samples from centre 2013, instead of the expected 25%, as distinct from the 25% positive for DP alone, 25% for SA alone and 25% neither for DP nor for SA.

DP plasma levels were either trace amounts (58 out of 90 samples) or extremely high values (> 150µg/ml; 32 out of 90 samples). These values were strikingly different from those observed in the other clinical centres; the high values from centre 2013 are in fact completely incompatible with pharmacokinetic data of the clinical use of DP (plasma levels do not exceed 5 µg/ml after oral administration).

Plasma SA levels originating from centre 2013 were also completely different from those coming from other centres and incompatible with the low dose ASA treatment regimen in the study.

Since serious doubt arose as to whether the plasma samples from centre 2013 were flawed, additional independent analysis of plasma protein polymorphism (Gm-Km-Hp-Gc-ABO) was conducted. Strikingly the laboratory report concludes that each of the 90 plasma samples sent by the centre is composed of the same mixture of plasma from several persons.

In addition, the last intake times reported by the trialist were again so precise (100% of the subjects took their last medicine between 6 and 12 AM on the day of plasma sampling) to arouse suspicion. Furthermore the time intervals between drug intake and plasma sampling were not compatible with the plasma DP and SA measurements.

The ESPS2 Steering Committee excluded this center while the study was still running and blinded.

C) Baseline Characteristics

Baseline characteristics for the modified ITT population

Study Group→	Placebo	ASA	DP	DP+ASA
Characteristics ↓				
Patient number	1649	1649	1654	1650
Mean age (years)	66.6	66.8	66.7	66.8
Males %	57.7	58	58.3	57.9
Females %	42.3	42	41.7	42.1

Reviewer's table

More males than females participated in the study. Exceptions to this trend occurred for patients older than 69 with a TIA as a qualifying event where more females were recruited and for patients older than 79 with stroke as a qualifying event where again more females than males were recruited.

Country of origin

Fifty-nine centers within thirteen countries contributed the 6602 patients for this study. No country contributed more than 25% of the patients. The Netherlands and UK each contributed 20%. Finland contributed 14%.

Qualifying Event

TIA was the qualifying event for 23.7% of the study population whereas stroke contributed the remaining 76.3%. In 80% of subjects a CT scan or MRI was performed. Pathological findings were detected in two-thirds of the examined patients. Nearly 52% of patients underwent cervical Doppler ultrasound. Abnormal results were detected in 36% of patients and these results gave support to the qualifying CVA in 49% of cases. Angiography was performed in 6.4% of patients with two-thirds of those subjects demonstrating an angiographic lesion consistent with the neurological deficit.

Quantification of the severity of residual damage persisting after the qualifying cerebrovascular event was assessed by means of a modified Rankin scale (R96-0263), whenever applicable. The definitions for the modified Rankin criteria are detailed in Appendix 1.

Distribution of patients in the Bamford clinical subclasses of stroke was not well matched (overall Chi-squared tests: $p < 0.001$). Bamford classification is detailed in Appendix 1. Stroke patients in the POCI subgroup were not equally distributed over the four treatment groups.

Comparison of Treatment Groups: Qualifying Event

	Placebo	ASA alone	DP alone	DP+ASA	P value (only if significant)
Number of patients	1649	1649	1654	1650	
Qualifying CVA					
TIA	379	392	388	403	
Stroke	1270	1257	1265	1246	
Missing Information	0	0	1	1	
History of vascular events prior to the qualifying CVA					
TIA pts. <12 mos.	123	120	108	116	
TIA pts.≥ 12 mos.	72	63	68	66	
Total # (% of subjects)	195 (11.8%)	183 (11.1%)	176 (10.6%)	182 (11.0%)	
Stroke pts. <12 mos.	192	174	151	163	
Stroke pts. ≥ 12mos.	182	184	189	159	
Total # (% of subjects)	374 (22.7%)	358 (21.7%)	340 (20.6%)	322 (19.5%)	
Bamford Clinical classification (% of classified patients)					
*TACI(4%)	45	59	41	53	
*PACI(33%)	365	394	384	411	
*LACI(39%)	463	431	450	465	
*POCI(24%)	301	284	309	227	<0.01
Total # (% of treatment group)	1174 (92.4%)	1168 (92.9%)	1184 (93.6%)	1156 (92.8%)	
Modified Rankin scale (% of classified patients)					
0 (11%)	147	132	132	131	
1 (34%)	428	401	444	439	
2 (24%)	296	329	309	294	
3 (14%)	192	177	169	179	
4 (16%)	193	209	202	191	
5 (0.8%)	12	9	9	12	
Total # (% of treatment group)	1268 (99.8%)	1257 (100%)	1265 (100%)	1246 (100%)	

Reviewer's table
*Abbreviations
Total Anterior Circulation Infarcts (TACI)
Partial Anterior Circulation Infarcts (PACI)
Lacunar Infarcts (LACI)
Posterior Circulation Infarcts (POCI)

The stroke distribution of patients with respect to the Bamford classification differs from the originally published paper. That classification scheme arose out of a prospective community study of stroke patients in the United Kingdom. The distribution of original Bamford study patients were as follows: 17% had TACI, 34% had PACI, 24% had POCI, and 25% LACI. The prospective study concluded that patients in the TACI subgroup had a high mortality predominantly due to immobility. Patients classified in the PACI subgroup were much more likely to

have an early recurrent stroke than other patients were. Patients classified in the POCI group were at greater risk of a recurrent stroke later in the first year following the initial event.[2]
The largest number of patients in ESPS 2 were classified in the LACI subgroup which had the lowest mortality and was associated with the lowest risk of recurrence. Of the 5038 patients with stroke as the qualifying event, the Bamford classification was assigned to 4682 patients. The remaining patients had either a recurrent stroke (n=279, 5.5%) or unclassified (n=77, 1.5%).

Risk Factors

Risk Factors from the clinical trial report

TABLE 8.3.3: 1. ASSOCIATED RISK CONDITIONS FOR RECURRENT STROKE
Source data: appendix 15.9.2.StAn.2: Demographic and Baseline Data

Associated conditions (in order of declining frequency)	Number (%) of patients with: TIA	stroke	TIA or stroke
Hypertension	865 (55.4)	3131 (62.1)	3996 (60.5)
Ischaemic heart disease*	452 (29.0)	1866 (37.0)	2319 (35.1)
Previous CVA	615 (41.2)	1209 (25.2)	1824 (29.0)
Smoking	393 (25.2)	1198 (23.8)	1591 (24.1)
Hypercholesterolaemia	395 (25.3)	1114 (22.1)	1509 (22.9)
Peripheral vascular disease**	333 (21.3)	1121 (22.3)	1454 (22.0)
Diabetes	156 (10.0)	855 (17.0)	1011 (15.3)
Gastrointestinal diseases	148 (9.5)	486 (9.6)	634 (9.6)
Cardiac failure	104 (6.7)	451 (9.0)	555 (8.5)
Atrial fibrillation	49 (3.2)	379 (7.6)	428 (6.5)
Alcohol consumption***	60 (3.8)	307 (6.1)	367 (5.6)
Other relevant diseases	357 (22.9)	1433 (28.4)	1790 (27.1)

*Defined by history or ECG evidence of ischaemia or infarction. **Defined by history, absence of femoral or popliteal pulse, or presence of femoral murmur. *** More than 5 units per day

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TABLE 8.3.3: 2. RISK FACTOR DISTRIBUTION IN THE TREATMENT GROUPS
Source data: appendix 15.9.2.StAn.2: Demographic and Baseline Data

Risk factor subgroup	Treatment group: placebo N = 1649	ASA 1649	DP 1654	DP-ASA 1650	p*
Hypertension: TIA	208	218	222	217	0.96
Stroke	814	765	790	762	0.11
Hypercholesterolaemia	347	377	375	410	0.08
Ischaemic heart disease	577	571	598	573	0.74
Atrial fibrillation	107	104	114	104	0.89
Cardiac failure	138	134	143	140	0.86
Peripheral vascular disease	363	362	372	358	0.95
Diabetes: IDDM	53	58	49	50	
NIDDM	186	182	229	204	0.28
Smoking (currently)	386	388	395	422	0.77
Alcohol (> 5 u/day)	96	87	100	84	0.59
Coffee (> 5 cups/day)	189	186	206	190	0.72

* Chi² test for the homogeneity of proportions in the four treatment groups.

TABLES 8.3.3: 3 to 8.3.3: 9 give more details about the various risk factors for TIA and stroke. Data are presented for the whole study population, and for the four geographic regions: Scandinavia (1665 patients; 25.2% of the total); Northwestern Europe (2425 patients; 36.7%); Southern Europe (1075 patients; 16.3%); and the UK & Ireland (1437 patients; 21.8%).

Stroke patients more often had ischemic heart disease or diabetes as a risk factor than patients presenting with TIA ($p<0.001$). Patients with a qualifying event of TIA were more likely to have a history of a previous CVA than patients with stroke ($p<0.001$).
There was a trend toward imbalance in hypercholesterolemia with more patients in the DP+ASA group. Similarly there was a trend toward imbalance for patients with the qualifying event of stroke in this subcategory there were more patients with a history of hypertension in the placebo group.

Regional information was presented in tabular form for the following baseline medical conditions: hypertension, ischemic heart disease, cardiac failure, atrial fibrillation, diabetes mellitus, hypercholesterolemia, smoking, coffee, and alcohol consumption. There were no clinically relevant regional differences in systolic or diastolic blood pressure, however patients from Southern Europe tended to have lower pressures.
Ischemic heart disease was more prevalent in the United Kingdom and Ireland, however age may have been a contributing factor, as patients in these two countries tended to be older. Ischemic heart disease was more common in those patients with stroke than in patients with TIA as a qualifying event (37% vs. 29% respectively). Cardiac failure and atrial fibrillation were more prevalent in the United Kingdom and Ireland, Northwestern Europe, and Scandinavia than Southern Europe.
Diabetes mellitus and hypercholesterolemia were lower in the United Kingdom and Ireland than other regions. Smoking information did not show any significant trends. Alcohol consumption (i.e. > 5 units per day) tended to be higher in Southern Europe. Coffee consumption demonstrated mild regional differences with higher amounts of consumption in Scandinavia and Northwestern Europe.

Concomitant Therapy

Information on concomitant medication was obtained primarily through check boxes, which were limited in detail. *If anticoagulant treatment became necessary, this was recorded in the CRF, and trial medication was stopped. Paracetamol (acetaminophen) was recommended for analgesia if necessary. Prescription of all other antiplatelet or non-steriodal anti-inflammatory drugs would require discontinuation of the trial regimen.* No information is provided about the duration of any concomitant medication. Panel 8.8.2.5:1 provides limited information regarding concomitant therapy.

PANEL 8.8.2.5:1 Summary of New Concomitant Medications Reported
ESPS2 – Intent-to-Treat Population

	Treatment Group				
Concomitant Medication	DP 200 mg/ ASA 25 mg b.i.d. n (%)	DP 200 mg b.i.d. n (%)	ASA 25 mg b.i.d. n (%)	Placebo n (%)	Overall n (%)
Total Number of Patients	1650	1654	1649	1649	6602
ASA (Other than Study Drug)	290 (17.6%)	362 (21.9%)	262 (15.9%)	297 (18.0%)	1211 (18.3%)
Antiplatelet	67 (4.1%)	68 (4.1%)	64 (3.9%)	79 (4.8%)	278 (4.2%)
NSAID	142 (8.6%)	133 (8.0%)	111 (6.7%)	130 (7.9%)	516 (7.8%)
Anticoagulant	64 (3.9%)	82 (5.0%)	89 (5.4%)	90 (5.5%)	325 (4.9%)

Note DP = Dipyridamole; ASA = Acetylsalicylic acid; DP+ASA = AGGRENOX™; NSAID = Non-steroidal anti-inflammatory drug.
Reference: Table 1.5.0
Sponsor's table

The most frequently reported new concomitant medications were ASA other than the study drug (18.3%) and non-steroidal anti-inflammatory drugs (7.8%). During any single visit interval, at most 5.9% of the patients in the DP+ASA and DP alone treatment groups and 4.1% of the patients in the ASA-alone and placebo treatment groups took at least one dose of ASA.

Study Plan

Treatments
All medication was given orally and supplied by Dr. Karl Thomae GmbH laboratories. Drugs were supplied in packs and labeled with the personal number assigned to the patient. Each pack supplied enough capsules for 6 months of treatment plus 4 additional weeks. The pills were given every 12 hours for 2 years. The protocol permitted temporary dose reduction if treatment was poorly tolerated.

Blinding
The blinding was preserved through the use of identical capsules for the placebo and study drug groups. Neither the investigator nor patients were provided information about their treatment. Study personnel including trialist, clinical monitor, statistician, data management, and data entry personnel were blinded until data base lock, August 1, 1995.

Drug Exposure and Treatment Compliance
Duration of treatment was calculated as the number of days between the dates of treatment randomization and treatment cessation. The mean duration of treatment was greater in those treated with ASA alone and placebo (559 and 540 days, respectively) compared with those treated with DP+ASA and DP (507 and 502 days, respectively).
In addition to patient recall and pill count, an assessment of plasma DP and ASA concentrations by a central expert laboratory was performed in a random subset of patients. This evaluation involved 15% of the patient population. Approximately 1000 plasma samples were taken during follow up evaluation from patients to measure blood DP and/or SA concentrations. Results are shown below.

TABLE 10.1.2: 1. COMPLIANCE: PLASMA SA AND DP CONCENTRATIONS
Source data: appendix 15.9.2.StAn.5 : Safety Data

Plasma drug determination	Number of plasma samples taken for concentration measurement				
	Placebo	ASA	DP	DP-ASA	Total
DP: Negative	266	240	11	5	522
DP: Positive	4	7	242	222	475
total:	270	247	253	227	997
compliance = 97%					
SA: Negative	235	48	218	48	549
SA: Positive	28	192	27	174	421
total:	263	240	245	222	970
compliance = 84%					
SA*: Negative	225	30	194	26	475
SA*: Positive	28	189	26	170	413
total:	253	219	220	196	888
compliance = 88%					

* SA determinations only considered for plasma samples taken within 9 hours after the last drug intake.

Sponsor's table

DP-determinations gave results predicted by treatment in 970/997 suggesting a compliance level of 97%. SA-determinations gave results suggesting a compliance level of 84%. Further investigation suggested that among the other potential contributions the length of time between ASA intake and plasma sampling may be too long given the low dose of ASA (i.e. more samples may be positive but below the lower limit of detection by the assay method). Using only those samples obtained less than 9 hours after ASA intake the SA compliance level was 88%.

At the occurrence of endpoints special forms (appendices in the case report forms) were filled out. These forms included the stroke report form, death report form, myocardial report form, and vascular events report form.

Study monitoring/Audits

On-site monitoring was performed four times per year at least. Centers contributing larger numbers of patients than average were visited more frequently. Source data checks were performed in a subgroup of 10-20% of patients selected at random by computer for each center.

Data audits were performed at regular intervals throughout the duration of the study. Process audits were carried out at all sites involved in the production, packaging and distribution of the trial medication:

the drug supply center
the TSU (Technical Support Unit)
the eight study centers that recruited the largest number of patients
the sponsor's operating units corresponding to the selected study cehtres.

The audit certificates are provided in vol. 1.121.

Efficacy Assessment

The MMAG assessed all endpoints and vascular events on a blinded basis. The group also reviewed possible protocol deviations and violations.

MMAG provided clarification of endpoint definitions.

Primary endpoint definitions:

1) Death – death from any cause occurring within 2 years of inclusion, i.e. before day 731 after randomization
2) Sudden death – death of unknown cause, occurring less than 24 hours after the onset of symptoms; sudden deaths are to be considered vascular deaths in the outcome analysis
3) Stroke – stroke occurring within 2 years after inclusion (includes all categories, since infarction and hemorrhagic stroke are sometimes difficult to distinguish on the basis of clinical symptoms alone)
4) Fatal stroke – stroke assessed as the primary cause of death (i.e. death occurs within 30 days of stroke)
5) Fatal MI – MI assessed as primary cause of death (i.e. death occurs within 30 days of MI)

Secondary endpoint definitions:

1) MI (fatal or non-fatal)
2) TIA
3) Ischemic events (combined endpoint, including all patients who had a stroke and/or a myocardial infarction and/or died abruptly (sudden death))
4) Other vascular events (OVE: combined endpoints, including all patients who had pulmonary embolism, deep venous thrombosis, peripheral arterial occlusion, retinal vascular accidents, or a combination of these events)
5) Vascular death (combined endpoint, including fatal stroke, fatal myocardial infarction, death due to other vascular events or cardiac failure, sudden deaths listed as of unknown cause, hemorrhagic deaths (non-cerebral fatal bleeding))
6) Vascular events (combined endpoint, including vascular death, non-fatal stroke, non-fatal myocardial infarction, and non-fatal other vascular event)

Additional Guidelines provided during the study:

1) Global amnesia –rare TIA thus could be a qualifying event
2) Vascular ophthalmological syndromes related to retinal arterial thrombosis as CVA: either TIA or stroke
3) Subdural hematomas and arachnoid hemorrhage considered as hemorrhages rather than strokes
4) Carotid endarterectomies were recorded as serious adverse events rather than vascular events.

Statistical Analysis

From the clinical trial report, *ESPS 2 was designed to achieve a study power of 80% (the likelihood of detecting at the 5% level a treatment effect, i.e. a Risk Reduction (RR) of at least 30% between the best and worst treatments). Computations, based on assumptions derived from ESPS 1, suggested that a sample size of 1250 per treatment group would be required to achieve this power; this critical number of patients per group was subsequently increased to 1750, when the statistical estimates were compared with the data emerging from the scheduled interim analysis. Impact of the interim statistical analysis on the acceptance level of statistical significance during the final analysis was negligible, since the protocol prescribed that the study should only be interrupted when interim effects were observed at the $p<0.001$ level.*

ESPS 2 has a factorial design, so that the two treatments (ASA and DP) are each statistically considered at two levels: present or absent. This design allows assessment of:

the effect of ASA (based on a comparison between the placebo and DP treatment groups versus the ASA and DP-ASA treatment groups , each with 3500 (patients)

the effect of DP (based on a comparison between placebo and DP-ASA treatment groups, each with 3500 patients)

the effect of the interaction between ASA and DP (based on a comparison between the placebo and DP-ASA treatment groups versus the ASA and DP treatment groups, each with 3500 patients).

Analysis of ESPS 2 data (baseline and endpoints) comprised the following statistical techniques:

Comparisons within groups via descriptive analysis, cross-tabulation and analysis of variance.

Primary and secondary endpoint data were mainly analysed via "survival" analysis.

In addition Cox's log linear model of proportional hazards was used to analyse the potential impact of covariates upon "survival".

Odds ratios have also been calculated, and, for some parameters Chi-square test were used.

The major null hypotheses were:

1. *Treatment with ASA does not prevent stroke and/or death*
2. *Treatment with DP does not prevent stroke and/or death*
3. *Treatment with DP-ASA does not prevent stroke and/or death*

The minor null hypotheses were:

1. *Treatment with ASA alone does not prevent stroke and/or death*
2. *Treatment with DP alone does not prevent stroke and/or death*
3. *Combination of DP-ASA is not more effective than ASA alone*
4. *Combination of DP-ASA is not more effective than DP alone*
5. *Low daily dosage of ASA is not associated with low incidence of adverse reactions*

Sample Size Issues

There is a discrepancy in the interim analysis issue from the original written protocol and statements made in the clinical trial report and the efficacy statements in the NDA. Although the NDA submission states amendments were made to the original protocol they were not provided in this submission. The original protocol in the statistical methodology section (enclosure 2) suggests that yearly interim analyses will be performed. Below is the original protocol.

13.5. Interim analysis

One interim analysis is foreseen 3 years after the beginning of the study or when 1600 patients reach two years of follow-up (which ever occurs earlier). The results of this interim analysis will be communicated to the Ethics Committee and might be the basis for a new assessment of the rationale of the trial by the Steering Committee.

From the clinical trial report, the sample size initially was chosen so that there would be 80% chance of detecting a genuine treatment effect at the $p<0.05$ level, if treatment leads to 30% risk reduction. The interim analysis was planned either 3 years from the start of patient recruitment or when 1600 patients had achieved 2 years of follow-up. Interim analysis with the 3795 patients recruited into the study suggested that each treatment group should contain 1750 patients, giving a total sample size of 7000. The protocol was amended to reflect that in 1992. This amendment was not submitted for review.

Data Analysis
Data analyses were conducted using intention-to-treat approach and results were reported both in terms of the number of events per group and "survival" curves (i.e. the percentage of patients that did not reach the relevant endpoint, which is different from actual death).

TABLE 9.3: 1. LIST OF ENDPOINTS AND SUBGROUPS IN "SURVIVAL ANALYSIS"

Endpoints:	Myocardial Infarction, all cases
Stroke, all cases	Myocardial Infarction, non fatal cases only
Stroke, non fatal cases only	Myocardial Infarction, fatal cases only
Stroke, fatal cases only, with patient withdrawn at time of a non fatal stroke	Ischaemic Event, all cases
	Ischaemic Event, non fatal cases only
Stroke, fatal cases only, without regard of a possible intercurrent non fatal stroke	Ischaemic Event, fatal cases only
	Other Vascular Event
Death, any causes	*Vascular Death*
Stroke and/or Death for any cause	Vascular Event
Subgroups:	Atrial fibrillation: yes
TIA as Qualifying Event (QE)	Atrial fibrillation: no
Stroke as QE	Diabetes: yes
Male	Diabetes: no
Female	Insulin-dependent diabetes (IDDM)
Male & TIA as QE	Non-Insulin-dependent diabetes (NIDDM)
Female & TIA as QE	Smoking
Male & Stroke as QE	No Smoking
Female & Stroke as QE	Alcohol consumption >5 units/day
CTScan or NMR: normal	Alcohol consumption ≤ 5 units/day
CTScan or NMR: abnormal	Regional groups: Scandinavia
CTScan or NMR: confirming	Regional groups: UK + Ireland
CTScan or NMR or Angio or Doppler: normal	Regional groups: North West Europe
CTScan or NMR or Angio or Doppler: abnormal	Regional groups: South Europe
CTScan or NMR or Angio or Doppler: confirming	Age: less than 60
Previous CVA: anytime	Age: higher or equal to 60
Previous CVA: older than one year	Hypertension: yes
Previous CVA: earlier than one year	Hypertension: no
Previous CVA: none	Diastolic blood pressure less than 90 mm Hg
Cerebral location :hemispheric	Diastolic blood pressure higher or equal 90 mm Hg
Cerebral location: brainstem	Systolic blood pressure less than 160 mm Hg
Cerebral location: hemispheric right	Systolic blood pressure higher or equal 160 mm Hg
Cerebral location: hemispheric left	Bamford classification: TACI
Cerebral location: uncertain	Bamford classification: PACI
IHD: yes	Bamford classification: LACI
IHD: no	Bamford classification: POCI
History of AMI or MI residual signs at ECG	

Sponsor's table from the clinical trial report

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Primary Endpoints

Treatment was given during the conduct of the trial that could effect patient's outcome for the primary endpoints. Carotid endarterectomies were performed during the course of the trial. These patients remained in the trial so the additional treatment they received may affect the results. Several patients received surgery prior to entrance into the trial. These patients were not randomized between the four treatment groups. Below is a table showing the distribution of patients who had a carotid endartectomy either prior to entry into the trial or during the trial.

Carotid Endarterectomies Prior to or During the Trial

Group	Number of Patients
Placebo	4
ASA	7
DP	4
DP+ASA	12

Reviewer's table

There are discrepancies from the information provided by the sponsor and the reviewer's analysis using JMP. Patients with the following numbers could not be found in the serious adverse event files, 20191223 and 23111392.

Clearly from the table above there are more patients in the combined treatment group who undergo carotid endartectomy and remain in the trial.

Ideally the primary analysis of efficacy data should reflect the intention-to-treat population, this includes those patients who were lost to follow up and patients from center 2013. For the sake of clarity, the term modified ITT population will mean the 6602 patients who were not part of the misdiagnosis/misinclusion category and who were not from center 2013. Wherever the sponsor has provided information about the inclusion of center 2013 and the patients who were lost to follow-up, these analyses will be clearly labeled.

Primary Endpoint Stroke and/or Death

This analysis represents the combined endpoint, which the sponsor is requesting as the indication for approval. This endpoint was not specified in the original protocol. There was no protocol amendment to reflect the combined endpoint. The clinical trial report and subsequent published papers and the efficacy section reflect this third endpoint.

Modified ITT

Primary Endpoint – Stroke and/or Death for modified ITT

After 24 months of treatment	Group 1 Placebo N=1649	Group 2 ASA N=1649	Group 3 DP N=1654	Group 4 DP+ASA N=1650	Total N=1650
Events	380	330	322	287	1319

Reviewer's table

"Survival" from stroke and/or death was markedly affected by treatment. There were 93 fewer events in the DP+ASA group than in the placebo group. Intermediate results were obtained in the ASA alone and DP alone groups. The results for stroke and/or death reflect the highly significant results for stroke, as there was no benefit from treatment for the endpoint of death. The Gehan-Wilcoxon Test P-values are listed below:

Statistical Analysis for the primary endpoint stroke and/or death (modified ITT)

Type of Analysis	P-value
Factorial Analysis	
DP vs. No DP	0.003
ASA vs. No ASA	0.002
DP x ASA Interaction	0.504
Pairwise Treatment Group	
DP 200mg/ASA 25mg vs. DP 200 mg	0.079
DP 200mg/ASA 25 mg vs. ASA 25 mg	0.084
DP 200 mg/ASA 25 mg vs. Placebo	<0.001
DP 200 mg vs. Placebo	0.012
ASA 25 mg. vs. Placebo	0.009

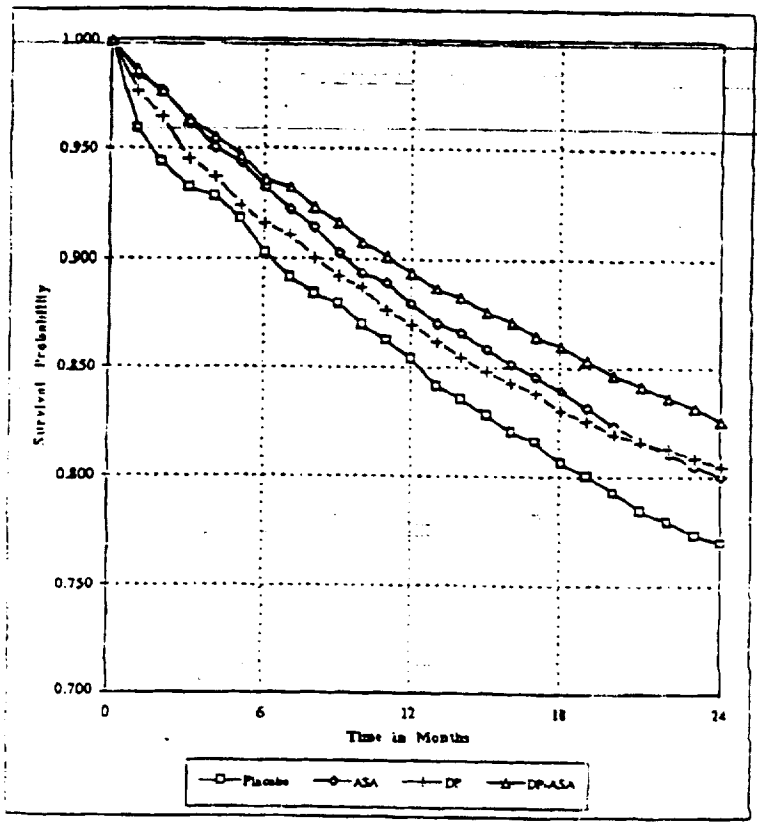
Reviewer's table from data provided by the sponsor

A statistically significant difference for the components was seen in the factorial analysis. The pairwise analysis provides the better assessment of whether the combination product provides additional benefit compared to the individual components. From the table above the combination product does not provide a statistically significant benefit over the individual components for the combined endpoint of stroke and death.

I am unable to locate the worst case analysis and inclusion of center 2013 for the combined endpoint of stroke and/or death.

Below is a survival graph of the effect of treatment on stroke and/or death for the modified ITT population.

FIGURE 9.3.1.3: 1. "SURVIVAL" CURVES FOR STROKE AND/OR DEATH
Source data: appendix 15.9.2.StAn.4: Efficacy / Pharmacodynamic Data



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Sponsor's graph

From the graph the combined treatment group has a better survival from stroke and death compared to placebo and the active treatment groups.

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Primary Efficacy Endpoint-Stroke (Fatal or Not)

Modified ITT

Stroke Prevention with ASA, DP, or DP+ASA (cumulative number of patients achieving the endpoint of stroke)

Months of treatment	Group 1 (Placebo) N=1649	Group 2 (ASA) N=1649	Group 3 (DP) N=1654	Group 4 (DP+ASA) N=1654	TOTAL N=6602
6	110	77	93	55	335
12	169	137	145	97	548
18	213	176	188	126	703
24	250	206	211	157	824

Reviewer's table from sponsor's information

The data presented above are consistent with a combined effect as those patients treated with either ASA or DP alone demonstrated stroke incidences that were an intermediate between the results with placebo and the results with combination treatment. *Differences in stroke prevention were already visible after six months of treatment with ASA or DP-ASA, while the greatest risk reduction obtained with DP appeared to be apparent somewhat later.* After six months of treatment, the differences between the four groups were significant (overall chi-square 19.7, $p<0.001$). There was 60% difference in the number of events at 24 months. Below is a table of the factorial and pairwise analysis for the endpoint of stroke.

Statistical Analysis for the primary endpoint of stroke (modified ITT)

Type of Analysis	P-value
Factorial Analysis	
DP vs. No DP	0.001
ASA vs. No ASA	<0.001
DP x ASA Interaction	0.850
Pairwise Treatment Group	
DP 200mg/ASA 25mg vs. DP 200 mg	0.002
DP 200mg/ASA 25 mg vs. ASA 25 mg	0.008
DP 200 mg/ASA 25 mg vs. Placebo	<0.001
DP 200 mg vs. Placebo	0.036
ASA 25 mg. vs. Placebo	0.009

Reviewer's table from data provided by the sponsor

The pairwise analysis for the endpoint of stroke suggests a statistically significant benefit is seen with use of the combination product.

Subgroup analysis for those with a qualifying event of TIA and those with a qualifying event of stroke suggested a similar trend.

Selected analysis of stroke in subgroups for modified ITT

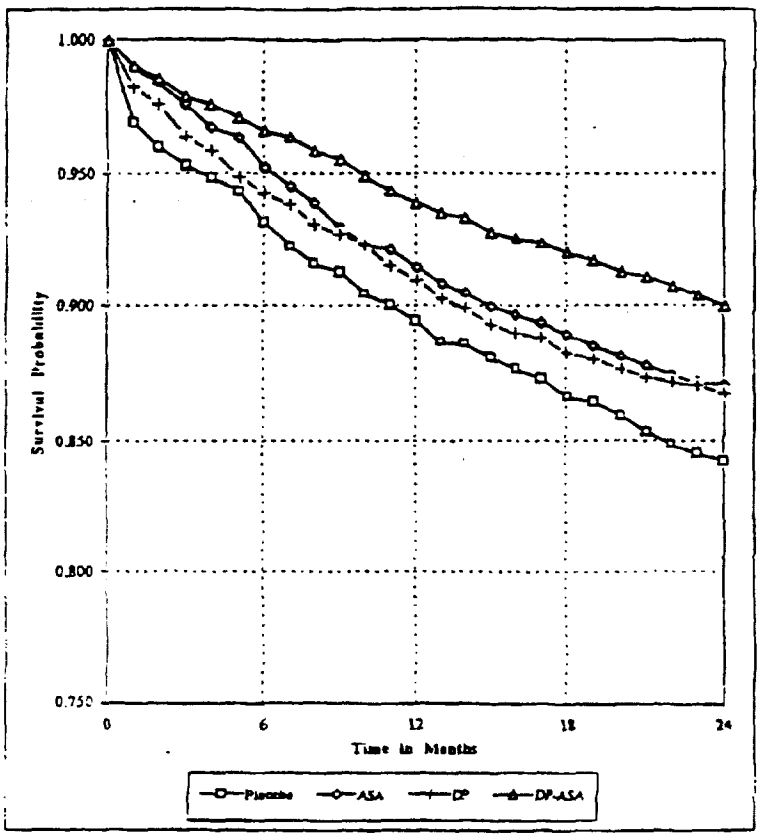
Subgroup	Placebo	ASA	DP	DP+ASA
Total patients with TIA as qualifying event (23.7%)	379	392	388	403
Patients with qualifying event = TIA who experience a stroke	46 (12.1%)	29 (7.4%)	35 (9%)	28 (7%)
Total patients with stroke as qualifying event (76.3%)	1270	1257	1265	1246
Patients with qualifying event = stroke who experience a stroke	204 (16.1%)	177 (14.1%)	176 (13.9%)	128 (10.3%)

Reviewer's table

The trial was not appropriately sized for a separate statement to be made about the efficacy of the combination product for patients with a qualifying event of TIA. The European definition of stroke includes TIA thus the trial was sized for the European definition. No further subset analysis can be made for these qualifying events.

Below is a plot of survival curves for each treatment group using the modified ITT population.

FIGURE 9.3.1.1: 1. "SURVIVAL" CURVES FOR STROKE (FATAL OR NOT)
Source data: appendix 15.9.2.StAn.4: Efficacy / Pharmacodynamic Data



From the graph above the patients who received the combination product had better "survival" at two years compared to placebo and the component drugs.

Randomized Population Including Center 2013

After 24 months of treatment	Group 1 (placebo) N=1758	Group 2 (ASA) N=1758	Group 3 (DP) N=1764	Group 4 (DP+ASA) N=1760	Total N=7040
Stroke	256	212	217	162	847

Reviewer's table

The inclusion of these patients does not change the results for the primary endpoint of stroke.

The endpoint of stroke demonstrates a statistically significant benefit in terms of survival for the combination of DP+ASA over its components.

Primary Efficacy Endpoint-Death (any cause)

The primary endpoint of death was not influenced by treatment for either the modified ITT or for the randomized population.
The tables and curves below are for modified ITT as there was not a significant difference between the modified ITT and randomized populations.

Modified ITT

Causes of Death listed by treatment groups for the modified population

TABLE 9.3.1.2: 2. CAUSES OF DEATH IN ESPS 2
Source data: appendix 15.9.2.Stat.4: Efficacy/Pharmacodynamic Data

MMAG Classified Cause of Death	Number of subjects who died during the 2 years of FU: Placebo	ASA	DP	DP-ASA	Total
1. CVA: cause = new stroke	43	39	56	38	176
CVA: cause = initial stroke	1	3	2	2	8
2. Myocardial Infarction	16	21	15	17	69
3. Cardiac Failure	12	11	9	7	39
4. Other Vascular Event**	8	3	4	7	22
5. Miscellaneous Vascular Event***	6	5	8	9	28
6. Bleeding*	2	1	2	4	9
7. Neoplasia	24	20	18	27	89
8. Infection	43	35	36	29	143
9. Other	11	9	9	12	41
10. Sudden Death	31	27	24	25	107
11. Unknown	5	8	5	8	26
Total	202	182	188	185	757

* For 25 additional patients with clinical diagnosis of fatal bleeding, the primary cause of death (e.g. fatal haemorrhagic stroke, rupture of aortic aneurysm, gastric cancer or gastric ulcer) was classified by the MMAG as one of the other indicated categories. Details for these patients are given in table STAn.5.3.2 (statistical report).
** Defined according to the protocol as one of the four following conditions: deep venous thrombosis, pulmonary embolism, peripheral arterial occlusion or retinal vascular accident.
*** Classified by the MMAG as other vascular event (eg rupture of aortic aneurysm, acute cardiac failure or ischaemic/arrest disease), but not belonging to the four clinical conditions defined by the protocol.

Below is a table of the factorial and pairwise analysis.

Statistical Analysis for the primary endpoint of death (modified ITT)

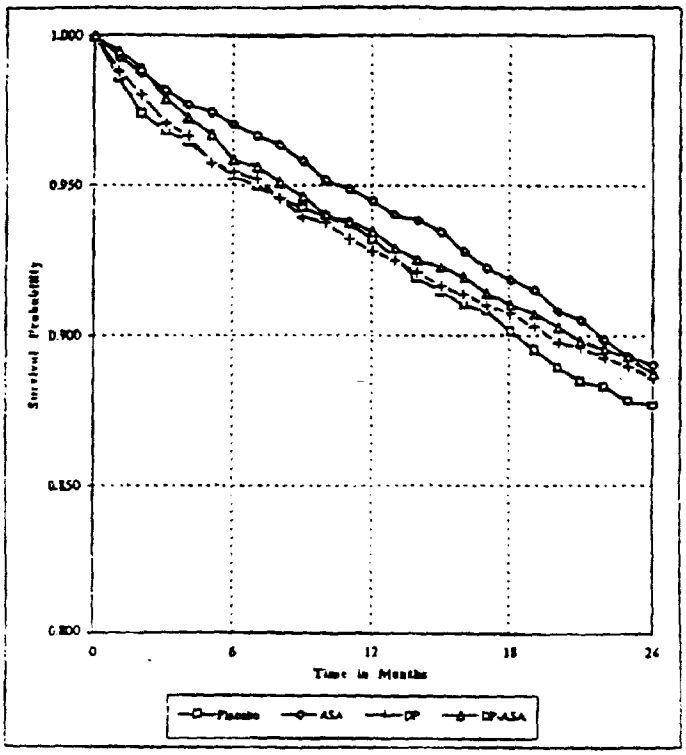
Type of Analysis	P-value
Factorial Analysis	
DP vs. No DP	0.732
ASA vs. No ASA	0.287
DP x ASA Interaction	0.461
Pairwise Treatment Group	
DP 200mg/ASA 25mg vs. DP 200 mg	0.815
DP 200mg/ASA 25 mg vs. ASA 25 mg	0.777
DP 200 mg/ASA 25 mg vs. Placebo	0.324
DP 200 mg vs. Placebo	0.453
ASA 25 mg. vs. Placebo	0.204

Reviewer's table from data provided by the sponsor

There is no benefit for either the combined product or its components over placebo.

Survival Curves for death from any cause for the modified ITT population

FIGURE 9.3.1.2: 1. "SURVIVAL" CURVES FOR DEATH (FROM ANY CAUSE)
Source data: appendix 15.9.2.StAn.4: Efficacy / Pharmacodynamic Data



Sponsor's graph

Looking at the table and the graph, the outcome of death was not influenced by treatment.

Overview of Primary Efficacy Endpoints

The next two summary tables are from the clinical trial report and aid in the evaluation of the effectiveness of the combination product versus its components.

Factorial Analysis of endpoints from the clinical trial report (modified ITT)

TABLE 9.3.1.4: 1. FACTORIAL ANALYSIS OF MAJOR ENDPOINT DATA
Source data: appendix 15.9.2.StAn.4: Efficacy / Pharmacodynamic Data

Factor analysed	number of patients with endpoint (number of patients analysed)					
	STROKE		DEATH		STROKE and/or DEATH	
ASA effect						
ASA treated	363 (3299)	p<0.001	367 (3299)	p=0.3	616 (3299)	p=0.003
non-ASA treated	461 (3303)		390 (3303)		699 (3303)	
DP effect						
DP treated	368 (3304)	p<0.001	373 (3304)	p=0.7	607 (3304)	p=0.002
non-DP treated	456 (3298)		384 (3298)		708 (3298)	
interaction effect						
DP-ASA or placebo	407 (3299)	p=0.8	387 (3299)	p=0.5	664 (3299)	p=0.6
ASA or DP treated	417 (3303)		370 (3303)		651 (3303)	

Looking at the factorial analysis, both ASA and DP were effective in preventing the endpoints of stroke and stroke and/or death. The interaction effect comparing the mean of the placebo and DP+ASA groups with the mean of the ASA alone and DP alone groups was virtually the same suggestive of the additive effect exerted by ASA with DP.

Pairwise Analysis of the endpoints from the clinical trial report (modified ITT only)

TABLE 9.3.1.4: 2. PAIRWISE COMPARISONS OF THE MAJOR ENDPOINT DATA
Source data: appendix 15.9.2.StAn.4: Efficacy / Pharmacodynamic Data

Comparison:	number of patients with endpoint (number of patients analysed) STROKE		DEATH		STROKE and/or DEATH	
ASA vs Placebo						
ASA treated	206 (1649)	p<0.02	182 (1649)	p=0.2	330 (1649)	p<0.02
Placebo	250 (1649)		202 (1649)		378 (1649)	
DP vs Placebo						
DP treated	211 (1654)	p<0.04	188 (1654)	p=0.5	321 (1654)	p<0.02
Placebo	250 (1649)		202 (1649)		378 (1649)	
DP-ASA vs Placebo						
DP-ASA treated	157 (1650)	p<0.001	185 (1650)	p=0.3	286 (1650)	p<0.001
Placebo	250 (1649)		202 (1649)		378 (1649)	
DP-ASA vs ASA						
DP-ASA treated	157 (1650)	p<0.01	185 (1650)	p=0.8	286 (1650)	p=0.06
ASA treated	206 (1649)		182 (1649)		330 (1649)	
DP-ASA vs DP						
DP-ASA treated	157 (1650)	p<0.01	185 (1650)	p=0.8	286 (1650)	p=0.07
DP treated	211 (1654)		188 (1654)		321 (1654)	

The pairwise analysis is the more appropriate analysis when looking at the effect on endpoints for the combination product. For the endpoint of stroke, treatment with ASA alone (p<0.02 vs. placebo) and with DP alone (p<0.04 vs. placebo) appear effective. The effectiveness of the combination drug product for stroke was statistically significant compared to the components. For stroke and/or death, treatment with ASA alone (p<0.02 vs. placebo) and with DP alone (p<0.02 vs. placebo) appeared less effective than treatment with DP+ASA (p.001 vs. placebo). The effectiveness of the combination drug product for stroke and/or death was not statistically significant compared to ASA alone and DP alone.

Secondary Endpoints

Secondary Endpoints-Myocardial Infarction

Neither treatment with DP nor ASA resulted in a significant reduction in the incidence of myocardial infarction. The number of patients treated with aspirin who experienced a myocardial infarction was slightly lower.

Secondary Endpoint-Ischemic Events

Number of Ischemic Events from the clinical trial report (modified ITT)

TABLE 9.3.1.8: 1. NUMBER OF ISCHAEMIC EVENTS
Source data: appendix 15.9.2.StAn.4: Efficacy / Pharmacodynamic Data

Variable after 24 months of treatment	Group 1 Placebo N = 1649	Group 2 ASA N = 1649	Group 3 DP N = 1654	Group 4 DP-ASA N = 1650	Total N = 6602
Total number of patients with endpoint	307	266	271	206	1050
number of patients with:					
fatal ischaemic events	90	88	95	80	353
non-fatal ischaemic events	249	203	212	153	817

This secondary endpoint is significantly affected by the primary endpoint of stroke. The total number of patients with endpoints does not equal the number of patients with fatal ischemic events and non-fatal ischemic events because some patients had more than one endpoint.

The total number of patients experiencing an ischemic event was significantly affected by the treatment regimen. Factorial analysis demonstrated both ASA ($p<0.001$) and DP ($p<0.001$) significantly prevented patients from suffering an ischemic event. Pairwise analysis demonstrated that the effects of ASA alone and DP alone achieved borderline significance while DP+ASA was significantly more effective than ASA alone ($p=0.003$), DP alone ($p=0.001$), or placebo ($p=0.001$). Treatment did not appear to affect the subgroup of patients suffering fatal ischemic events.

Secondary Endpoint-Other Vascular Events (OVE)

Other Vascular Events from the clinical trial report (modified ITT)

TABLE 9.3.1.9: 1. NUMBER OF OTHER VASCULAR EVENTS (OVE)
Source data: appendix 15.9.2.StAn.4: Efficacy / Pharmacodynamic Data

Variable after 24 months of treatment	N=	Placebo 1649	ASA 1649	DP 1654	DP-ASA 1650	Total 6602	p
Number of patients with OVE		54	38	35	21	148	**
"Survival" (%)		96.5	97.6	97.8	98.7	-	
Risk reduction (%)		-	31.6	36.7	61.7	-	
‰ Persons saved from endpoint		-	11.0	12.8	21.5	-	
Subgroups: number of OVE patients with:							
deep venous thrombosis		21	15	15	6	57	-
pulmonary embolism		14	14	11	10	49	
peripheral arterial occlusion		21	11	10	6	48	*
retinal vascular events		1	2	2	1	6	

p-values: overall significance of treatment effect assessed by χ^2-tests (for the homogeneity of proportions in the four treatment : * = $p < 0.05$; ** = $p < 0.01$)
In 12 patients a combination of at least two OVE conditions occurred: deep venous thrombosis plus pulmonary embolism (11 patients) or deep venous thrombosis plus peripheral arterial occlusion (1 patient).

Despite the small number of patients experiencing other vascular events, there was a tendency for decreased events in the treated groups, particularly the patients in the DP+ASA group.

Secondary Endpoints-Vascular Deaths

The total number of patients who died because of a vascular event includes those listed in the table as well as death due to cardiac failure, unknown cause, and hemorrhagic deaths (non-cerebral fatal bleeding). This table merely illustrates that treatment did not affect fatal clinical outcome.

Vascular Deaths from the clinical trial report (modified ITT).

TABLE 9.3.1.10: 1. NUMBER OF VASCULAR DEATHS
Source data: appendix 15.9.2.StAn.4: Efficacy / Pharmacodynamic Data

Variable after 24 months of treatment	Group 1 Placebo N = 1649	Group 2 ASA N = 1649	Group 3 DP N = 1654	Group 4 DP-ASA N = 1650	Total N = 6602
Total number of patients with endpoint	124	118	125	117	484
number of patients with:					
fatal stroke	43	39	56	38	176
fatal MI	16	21	15	17	69

Secondary Endpoint-Vascular Events
This category includes all patients with vascular death, non-fatal stroke, non-fatal MI, and non-fatal OVE.

Vascular Events from the clinical trial report (modified ITT)

TABLE 9.3.1.11: 1. NUMBER OF VASCULAR EVENTS
Source data: appendix 15.9.2.StAn.4: Efficacy / Pharmacodynamic Data

Variable after 24 months of treatment	Group 1 Placebo N = 1649	Group 2 ASA N = 1649	Group 3 DP N = 1654	Group 4 DP-ASA N = 1650	Total N = 6602
Total number of patients with endpoint	361	314	324	246	1245
"Survival" (%)	77.7	80.7	80.1	84.7	
Risk reduction (%)	-	13.3	10.5	31.6	
‰ Persons saved from endpoint	-	29.6	23.5	70.3	

This composite endpoint demonstrated a significant benefit of treatment primarily because of the contribution of patients who did not suffer a fatal vascular event. Factorial analysis demonstrated both ASA (p=0.001) and DP (p=0.001) exerted independent effects.

Secondary Endpoint-Transient Ischemic Attack (TIA)

TIA is a protocol-specified secondary endpoint that was determined by experienced neurologists but was neither described in detail on the CRFs not reviewed by the MMAG.

Eighty-nine patients were not assessed for TIA during follow up.

This category is subject to significant recall bias and interpretation by both the patient and the physician due to the underlying nature of the disease.

Secondary Endpoint-TIA (modified ITT population)

Category	Placebo	ASA	DP	DP+ASA	Total
n =	1622	1631	1629	1631	6513
≥ 1 TIA reported	268 (16.5%)	206 (12.6%)	215 (13.2%)	172 (10.5%)	861

Reviewer's table

Below is the sponsor's table from the clinical trial report on TIA incidence during the trial for the modified ITT population.

TABLE 9.3.1.12: 1. TIA INCIDENCE, QUALIFYING EVENT AND TREATMENT
Source data: appendix 15.9.2.SAS.4: Efficacy / Pharmacodynamic Data

Category: number of TIA's during 2 years of FU	Number of patients falling within the specified category: Group 1 Placebo	Group 2 ASA	Group 3 DP	Group 4 DP-ASA	Total	statistical significance*
All patients**						
0	1355	1425	1413	1459	5652	p < 0.001
≥ 1	267	206	215	172	860	
1	189	161	157	126	633	
2	46	28	30	28	132	
≥ 3	32	17	28	18	95	
any category:	1622	1631	1628	1631	6512	
QE = TIA:						
0	270	314	317	337	1238	p < 0.001
≥ 1	102	74	66	64	306	
1	72	56	52	44	224	
2	16	9	3	10	38	
≥ 3	14	9	11	10	44	
any category:	372	388	383	401	1544	
QE = stroke:						
0	1085	1111	1096	1122	4414	p = 0.004
≥ 1	165	132	149	108	554	
1	117	105	105	82	409	
2	30	19	27	18	94	
≥ 3	18	8	17	8	51	
any category:	1250	1243	1245	1230	4968	

* Chi² test for the homogeneity of proportions in the four treatment groups.
** QE = TIA or Stroke; Detailed data on the numbers of TIA in table 9.3.1.12: 1 are based on the numbers of follow-up visits where the patient declared the occurrence of at least one TIA since the last visit.

Sponsor's table from the clinical trial report

No information was available for 90 patients. The missing information was evenly distributed over the four treatment groups. The missing information constituted less than 2% of the data for each treatment group. There was a decreased incidence of TIA reported with use of ASA, DP, or DP+ASA. The greatest decrease was observed in those patients receiving combination therapy. The risk of developing a TIA during follow up was higher for those individuals whose qualifying event was a TIA.
Statistical analysis using Factorial analysis and pairwise comparison are detailed below:

Statistical analysis for TIA (Intent-to-treat population)

Analysis Type	P-value
Factorial	
DP vs. No DP	0.002
ASA vs. No ASA	0.001
DP X ASA interaction	0.382
Pairwise Treatment Group	
DP 200 mg/ASA 25 mg vs. DP 200mg	0.022
DP 200 mg/ASA 25 mg vs. ASA 25 mg	0.104
DP 200 mg/ASA 25 mg vs. Placebo	0.001
DP 200 mg vs. Placebo	0.008
ASA 25 mg vs. Placebo	0.001

Reviewer's table from sponsor's analysis

Factorial analysis indicated that both ASA and DP were effective (both p≤ 0.002) and the component interaction was additive. Pairwise analysis does not indicate a statistically significant reduction in TIA incidence for the combination over ASA.

Subgroup Analyses

Subgroup Analysis

The subgroup analyses were reported as percent "survival" at 24 months, percent risk reduction, and persons saved by treatment in thousands. The term "survival" here means continuing in the trial without reaching an endpoint event. In most subgroup analyses, the combination product did not demonstrate a detrimental effect on survival. The subgroup of patients with Rankin score 5 had atypical results with some patients demonstrating a benefit on DP alone. These result are affected by the small numbers of patients entered into the trial with a Rankin score of 5. For ease of comparison I will only note any discrepancies.

Discrepancies in the subgroup analyses for percent survival at two years (>% 4 difference between combination product and other treatment groups)

Event	Placebo % survival	ASA alone % survival	DP alone % survival	DP+ASA % survival
Stroke:Rankin 5	73	73	100	90
Fatal-on-First stroke: Afib = yes	94	92	92	89
Fatal-on-First stroke: Rankin 5	80	100	100	90
Fatal Only stroke: Rankin 5	83	100	100	90
Death: Rankin 3	79	88	77	80
Death:Diabetes = yes	83	88	84	83
Myocardial infarction:IDDM	91	96	98	93
Fatal Myocardial Infarction:IDDM	94	96	98	93
Fatal Ischemic Event:Location Uncertain	100	95	97	95
Other Ischemic Events:Rankin 5	78	89	100	92
Vascular Death: MI history	82	78	90	84
Vascular Death: Diabetes yes	90	92	90	87
Vascular Death: IDDM	84	87	89	83
Vascular Death: NIDDM	91	93	90	88
Vascular Death:Rankin 3	84	92	83	84
Vascular Events: IDDM	67	69	78	72

Reviewer's table from sponsor's data